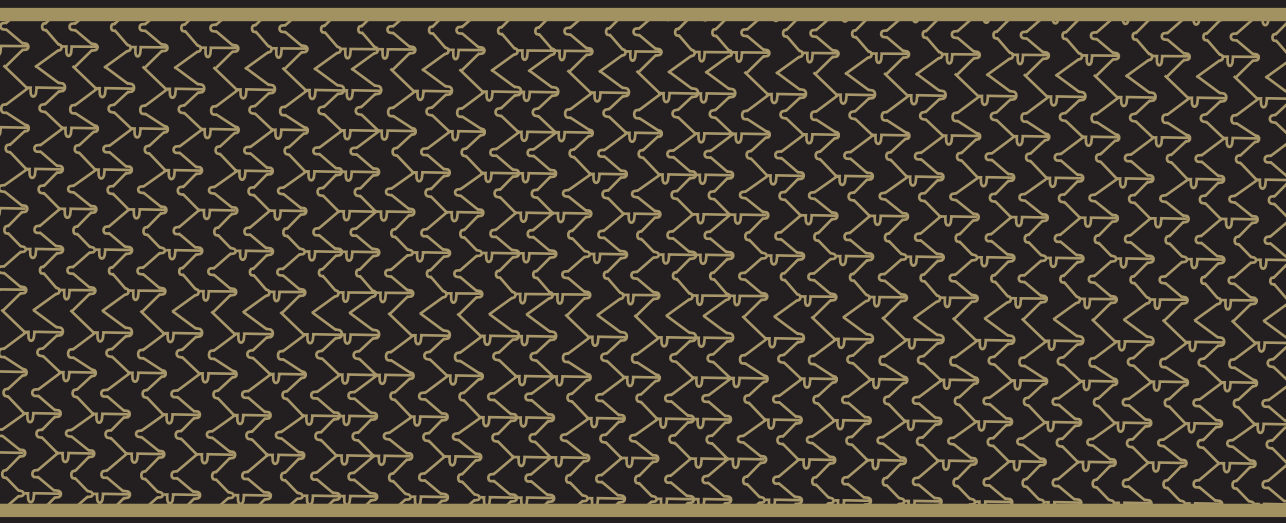
PERCUTANEOUS CORONARY INTERVENTIONS IN STABLE AND ACUTE CORONARY SYNDROMES

- STENT TECHNOLOGY, LESION COMPLEXITY AND CLINICAL OUTCOME



Michael **Magro**

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- stent technology, lesion complexity and clinical outcome

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Percutane coronaire interventies in stabiele en acuut coronaire syndromes – stent technologie, complexiteit laesie en klinische uitkomst

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To my parents and my wife Alexia

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Introduction

GENERAL OUTLINE OF THE THESIS

Percutaneous coronary intervention (PCI) has brought a major revolution in the way we manage coronary artery disease. Since the first intervention by Andreas Grüntzig in 1977 (1), development of the technology has been relentless and today PCI has been established as one of the major pillars of treatment of coronary heart disease alongside its medical and surgical solutions.

Stent implantation during PCI has given the needed edge to PCI, not only in restoring coronary flow but moreover in maintaining it (2). First generation drug eluting stents have effectively addressed the issue of re-stenosis, the Achilles heel of bare metal stents (3). However this came at cost of safety. The incidence of stent thrombosis with the drug eluting stents has shocked the medical community in a time when first generation DES use was spreading across all the spectrum of coronary syndromes, lesion complexities and at-risk patient populations (4). Further development of second generation DES with novel and iterative changes in the stent design, strut thickness, polymer and drug type and release were driven specifically to address caveats of the DES including the stent thrombosis issue (5,6). Particular interest was also shed on bifurcation stenting and development of dedicated systems aimed to improve outcomes in this difficult lesion subset (7).

Apart from effect of drug-eluting stent type, stent failure more often occurs in particular patient and lesion characteristics. Acute coronary syndrome, diabetes, bifurcation treatment and premature discontinuation of antiplatelet therapy and paclitaxel eluting stents were all implicated (8,9). The Syntax score, developed during the landmark coronary revascularization trial, the SYNTAX trial which compared PCI to CABG in patients with multivessel disease, quantifies the anatomical severity and importance of coronary artery disease (10,11). The score has been shown to be useful in risk stratification of patients and therefore in predicting adverse cardiovascular events and in guiding appropriate treatment in patients with stable coronary artery disease (12-14).

Percutaneous intervention in ST segment elevation myocardial infarction (STEMI), as in the stable coronary counterpart has long been established (15). Major differences in comparison with stable disease relate to the urgency of the procedure, the thrombotic environment and the underlying acute myocardial dysfunction. Restoration of epicardial coronary flow does not guarantee microvascular flow which has a direct impact on mortality in patients presenting with an acute myocardial infarction (16). Therefore adjunctive measures including thrombectomy and pharmacological treatment are often needed. Further insights into the effect of thrombus formation and of adjunctive treatment on epicardial and microvascular reperfusion are needed (17). Optical coherence

tomography (OCT) provides a unique way of analysing intracoronary thrombus and may therefore prove to be instrumenal to assess its significance.(18)

The aim of this thesis were to :

1. Determine the long term outcome of drug eluting stent implantation compared to bare metal stents in the general PCI population and explore clinical benefits of newer generation drug eluting stents.
2. Examine the clinical outcome of drug eluting stents in patient populations prone to aggressive coronary artery disease.
3. Analyse determinants and prognostic value of myocardial no reflow after stenting in acute myocardial infarction.
4. Utilize OCT to gain further insights into intra coronary thrombus and the effects for stenting and thrombectomy in patients with STEMI.
5. Establish the usefulness of the Syntax score in risk stratification of patients presenting with ST elevation myocardial infarction.
6. Assess the outcome of drug-eluting stent implantation in bypass grafts and evaluate a dedicated stent developed for bifurcation stenting including that of the left main stem.

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Part I

CORONARY STENTS

1.1

Drug eluting stents.

Garg S, Magro M, Serruys PW.

Chapter 232, textbook edited by E.Healy, Comprehensive Biomaterials Wiley-Blackwell 2010

6.627. Drug-Eluting Stents

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Abbreviations

BMS	Bare-metal stents
CAD	Coronary artery disease
CE	Conformité Européenne
DES	Drug-eluting stent
E-ZES	Endeavor Zotarolimus-eluting stent
EES	Everolimus-eluting stent
FDA	Food and Drug Administration
FIM	First In Man
IVUS	Intravascular ultrasound
mTOR	Mammalian target of rapamycin
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
PES	Paclitaxel-eluting stent
POBA	Plain old balloon angioplasty
QCA	Quantative coronary angiography
R-ZES	Resolute Zotarolimus-eluting stent
SES	Sirolimus-eluting stent
ST	Stent thrombosis
TLR	Target lesion revascularization
TVR	Target vessel revascularization

6.627.1. Introduction

The prevalence of ischemic heart disease is rising in line with increasing longevity of population, and the increased frequency of obesity, diabetes, and other coronary risk factors. Coupled with this is a lower threshold to investigate patients with symptoms suggestive of coronary artery disease (CAD), thereby increasing the importance of establishing an optimal form of treatment for patients with obstructive coronary lesions. Historically, owing to the problems associated with plain old balloon angioplasty (POBA) and the initial coronary stents, coronary artery bypass surgery was the preferred treatment in all but the simplest patient. In the past decade, new coronary stents have been developed which have revolutionized the ability to treat complex coronary lesions by percutaneous means. This chapter, after reviewing the problems associated with POBA and bare-metal stents (BMS), describes the first and second generation of drug-eluting stents (DESs), before finally reviewing some of the newer permanent stents which are currently being evaluated in on-going clinical trials.

6.627.2. The Need for Coronary Stents: Problems with Baloon Angioplasty and Bare-Metal Stents

The concept of wiring a diseased coronary artery and restoring luminal patency by means of a percutaneous approach has gone through extensive developments and advances since its first application in man by Andreas Grüntzig in 1977.[1] It has revolutionized the way we treat CAD and brought about a major shift from surgical to percutaneous intervention in all but the most severe and diffuse forms of the disease.[2]

POBA, the first form of percutaneous coronary intervention (PCI) relied on compression of atherosclerotic plaque through mechanical dilatation by balloon inflation. This process often caused vessel injury with tearing of the media. While chronic sequele in the form of vascular shrinkage (mediated by myofibroblasts, smooth muscle cells, and their proteoglycan and collagen secretions as well as elastic recoil) was a major concern, more sinister complications including abrupt vessel closure instigated the need for further development or alternatives of this technology.[3–5]

The use of a prosthetic device to improve vessel patency after POBA had already been proposed by Charles Dotter in 1964.[6] Two decades later, Puel implanted the first coronary stent – the Wallstent, a self-expanding metallic mesh.[7] The ability of such a device to cause and maintain a larger acute gain in luminal diameter proved to be key for its success, and the reason stents are implanted in the majority of PCIs performed today. The first stents to be implanted however were associated with a significant thombogenic risk which resulted in an 18% subacute stent thrombosis (ST) rate.[8] Measures to counteract this phenomenon, which included the introduction of complex anticoagulation regimens, resulted in an excess of vascular bleeding complications, and subsequent prolongation of hospitalization which altogether marred the initial successful results of the stenting concept when compared to POBA.[9]

Refinements in the stent system as seen in the landmark BENESTENT (BElgian NEtherlands STENT) (Figure 1)[10] and STRESS (STent REStenosis Study)[11] trials, as well as proof of the importance of adequate stent deployment,[12] redirected favorable light on the coronary stenting concept. Additionally, evidence that stenting was safe without need for anticoagulation through improvement in stent expansion and apposition, and with the use of dual antiplatelet therapy (DAPT), led to the exponential and widespread use of these early devices (Figure 2).[13–15]

The initial strengths and enthusiasm with the safer acute outcomes of stainless steel, cobalt–chromium alloy, and nitinol based stent implantation however met with what was described as the Achilles heel of BMS – in-stent restenosis (Figure 3). Neointimal growth mediated by smooth muscle hyperplasia and extracellular matrix produced significant luminal narrowing that peaked between 1 and 6 months after stent deployment.[16–18] As much as 20–40% of patients in whom

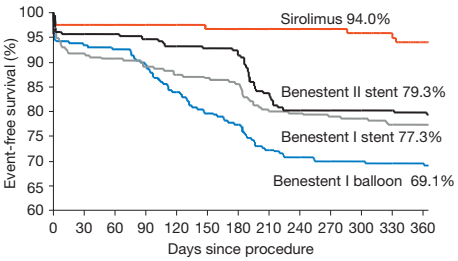

Figure 1 The improved event-free survival in the Benestent I and II trials with the use of a bare-metal stent (Benestent I stent) or a heparin coated stent (Benestent II) compared to only balloon angioplasty (Benestent balloon).[10] Event-free survival however is considerably greater with a sirolimus-eluting stent.

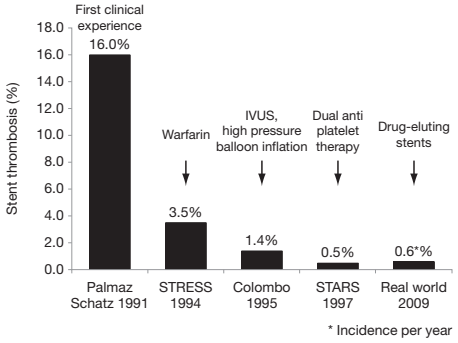

Figure 2 Temporal changes in the incidence of stent thrombosis following introduction of adjunct phamacotherapy, increased awareness of the importance of technique when implanting coronary stents, and the change from the use of bare-metal to drug-eluting stents. Adapted from Colombo, A.; Hall, P.; Nakamura, S.; *et al*. *Circulation* **1995**, *91*, 1676–1688; Leon, M. B.; Baim, D. S.; Popma, J. J.; *et al*. *N. Engl. J. Med*. **1998**, *339*, 1665–1671; Schatz, R. A.; Baim, D. S.; Leon, M.; *et al*. *Circulation* **1991**, *83*, 148–161; Fischman, D. L.; Leon, M. B.; Baim, D. S.; *et al*. *N. Engl. J. Med*. **1994**, *331*, 496–501; Wenaweser, P.; Daemen, J.; Zwahlen, M.; *et al*. *J. Am. Coll. Cardiol*. **2008**, *52*, 1134–1140.

these BMS were implanted, especially diabetic patients, those with small vessels and long lesions, presented with recurrence of anginal symptoms and angiographic restenosis (>50% diamenter stenosis). Restenosis rates, especially those confined to the stented part of the vessel (not including the 5 mm peristent segment) decreased dramatically after 6–12 months and this is attributable to replacement of the smooth muscle cells by a fibrotic matrix that halted further thickening of the neointimal layer.

Research efforts focusing on the neointimal proliferation phenomenon led to development of vascular brachytherapy, which employed beta or gamma sources to reduce in-stent restenosis.[19–22] Despite being shown to be effective in reducing recurrent stenosis by 30–70%, logistic problems associated with implementation of the treatment, recurrence of restenosis after 4 years[23] and the evolving concepts of using safer pharmacological agents instead of radiation, led to the downfall of this reparative technique.

Intravenous or oral antiproliferative, anti-inflammatory, or immunomodulatory agents failed to effectively reduce the neointimal hyperplasia in humans.[24] Attempts to increase local drug delivery by administration through porous angioplasty balloons also failed.[25,26] The possibility to link these bioactive substances to the stent surface itself and its release from the stent to the endothelium was then explored – DESs were born.

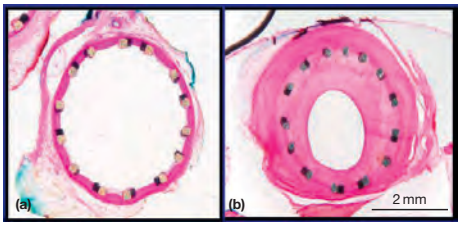

Figure 3 (a) Stent implantation in the porcine model demonstrating development of significant neointimal hyperplasia at follow-up (b).

6.627.3. Development of DESs

The first drug to be applied to coronary stents was in fact heparin, which was intuitively chosen to counter the thrombogenicity of BMS. Heparin-coated stents such as BX-Velocity Carmeda-coated stent (Johnson & Johnson, Warren, NJ), the Wiktor Hepamed-coated stent (Medtronic, Inc, Minneapolis, MN), and the Jostent Corline-coated stent (Jomed International AB, Helsingborg, Sweden) had their drug covalently bonded to the device, thereby significantly prolonging its presence on the stent.

Multiple drugs classes and types which inhibit restenosis by interference in pathways of inflammation and neointimal proliferation have been explored. These drugs can be classified as anti-inflammatory and/or immunomodulatory agents, antiproliferative agents, inhibitors of smooth muscle cell migration or extracellular matrix production, or promoters of healing and endothelialisation (**Table 1**).

The macrocylic lactone or 'limus' family of drugs which includes sirolimus, everolimus, biolimus A9, zotarolimus, tacrolimus, and pimecrolimus has been studied (**Figures 4** and **5**). The first four bind to the FKBP 12 binding protein which subsequently binds to the mammalian target of rapamycin (mTOR) and in doing so blocks the cell cycle mainly of the smooth muscle cell from the G1 to the S phase. Tacrolimus and pimecrolimus, on the other hand, bind to FKBP506 and form a complex which subsequently inhibits the calcineurin receptor, leading to decreased cytokine expression on the cell surface membrane. This results in inhibition of T cell activation and lower smooth muscle cell selectivity. Paclitaxel (**Figure 6**) is a nonlimus drug that stabilizes microtubules and thereby inhibits cell division in the G0/G1 and G2/M phases. It has also been applied to stents and thoroughly studied.

Table 1 A list of the various agents that were tested for potential application to drug-eluting stents

Anti-inflammatory, immunomodulators	*Antiproliferative*	*Smooth muscle cell migration inhibitors, extracellular matrix modulators*	*Promoters of healing and reendothelialization*
Limus family (sirolimus, everolimus, zotarolimus, biolimus A9, pimecrolimus)	Limus family (sirolimus, everolimus, zotarolimus, biolimus A9, pimecrolimus)	Batimastat	BCP671
Paclitaxel	Paclitaxel	Prolyl hydroxylase inhibitors	Vascular endothelial growth factor
Tacrolimus	Actinomycin D	Halofuginone	Estradiols
Cyclosporine	Methotrexate	C-proteinase inhibitors	Nitric oxide donors
Dexamethasone	Angiopeptin	Probucol	Endothelial progenitor cell antibodies
M-prednisolone	Vincristine		Biorest
Biorest	Mitomycine		Advanced coatings
Interferon gamma-1b	Statins		
Mycophenolic acid	CMYC antisense		
Mizorbine	RestenASE		
Tranilast	2-Chlorodeoxyadenosine		
	Proliferating cell nuclear antigen ribozyme		

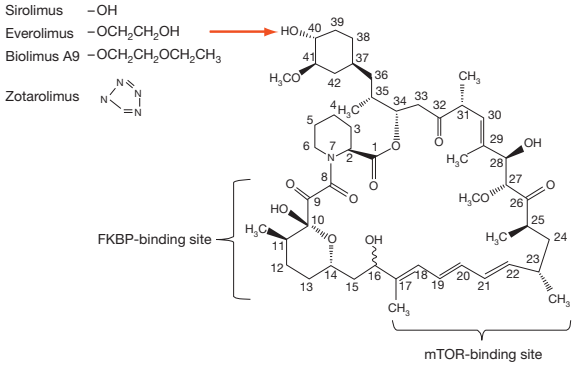

Figure 4 The macrocylic lactone or 'limus' family of antiproliferative agents. The different agents are derived following modifications to the macrocylic ring as shown. Their common mode of action includes binding to the FK-binding protein 12 (FKBP12), which in turn inhibits the mammalian target of rapamycin (mTOR) pathway. This subsequently prevents the down regulation of the cell division kinase inhibitor $p27^{kip1}$, thereby inhibiting cell division between phases G1 and S1 of the cell cycle.

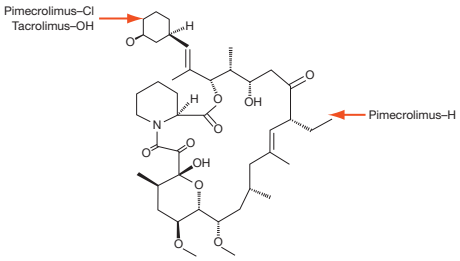

Figure 5 The chemical structure of tacrolimus and pimecrolimus.

Presently, only four DESs have been approved for use by the Food and Drug Administration (FDA). The first two DESs that were developed, the sirolimus-eluting and paclitaxel-eluting stent, are collectively known as first generation DESs, while the newer zotarolimus-eluting and everolimus-eluting stents are known as second generation DESs.

6.627.4. First Generation DESs

6.627.4.1. Sirolimus-Eluting Stent

Sirolimus was the first 'limus' agent to be used on a coronary stent (Figure 4). This macrolide antibiotic, produced by *Streptomyces hygroscopicus* has potent antifungal and antimitotic properties. It was discovered in Easter Island (Rapa Mui) in the South Pacific during an expedition in 1975 and was originally named rapamune to reflect its place of discovery. This highly lipophilic macrolytic lactone inhibits mTOR and exhibits potent antiproliferative and immunosuppressive effects. The first clinical application was as an immunosuppressive in renal transplant patients following FDA approval in 1999. The first sirolimus-eluting stent (SES) was the Cypher stent, developed by Cordis Corporation, Warren, NJ. It consisted of sirolimus in a concentration of 140 $\mu g\,cm^{-2}$, incorporated in an amalgam of two biostable polymers, with the polymer/drug matrix then applied onto the tubular 316L stainless steel BX-Velocity stent (Tables 2–4).

Both fast release stents with drug release in $<$15 days and slow-release stents with $\geq$28 days drug release were developed and tested in the 'First in Man' (FIM) study in 1999 in Sao Paulo, Brazil and Rotterdam, the Netherlands. Angiographic and intravascular ultrasound (IVUS) results from the 45 patients who were studied showed remarkable suppression of in-stent neointimal hyperplasia, which continued out to 4 years of follow-up (Figure 7).[27–29]

The pivotal RAVEL study (RAndomised study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) evaluated the Cypher SES by randomizing 238 patients with relatively low-risk lesions to treatment with SES or BMS. At 1-year follow-up the rate of binary stenosis was 0.0 and 26.6% for patients treated with Cypher SES and BMS, respectively.[30] These results were subsequently confirmed in the much larger SIRIUS trial (SIRolImUS-coated BX-Velocity balloon-expandable stent in the treatment of patients with de novo coronary artery lesions) that enrolled 1058 patients with more complex lesions than were seen in RAVEL. Significantly lower rates of target lesion revascularization (TLR) and major adverse cardiovascular events (MACE) following treatment with the Cypher SES were demonstrated when compared to BMS controls at 9-month, 2-year, and 5-year follow-up.[31–33] The Cypher stent was thus the first DES to receive Conformité Européenne (CE)-mark in April 2002 and was subsequently approved by the FDA in 2003.

Performance of the Cypher stent has been also assessed in 'off-label' situations and specific subgroups of patients such as diabetic patients,[34,35] and those presenting with ST-elevation myocardial infarction.[36,37] In addition, it has been assessed in patients with different lesion types including chronic total occlusions,[38,39] saphenous vein grafts,[40,41] lesions in small coronary vessels,[42,43] and complex lesions.[44,45]

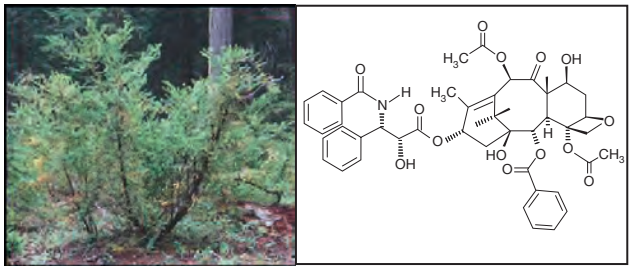

Figure 6 The antiproliferative agent paclitaxel, which is obtained from (a) the Pacific Yew tree, *Taxus brevifolia*. (b) The chemical structure of paclitaxel.

Table 2 Specifications of the first and second generation drug-eluting stents

Stent	*Drug (concentration)*	*Polymer*	*Polymer thickness (μm)*	*Release kinetics (28 days) (%)*	*Metal*	*Strut thickness (μm)*	*Crimped profile (mm)*[a]	*Max cell circumference/ diameter (mm)*[a]
CYPHER	Sirolimus (140 μg cm^{-2})	Polyethelyne-*co*-vinyl acetate and PBMA	12.6	80	SS	140	1.198	9.5/3.0
TAXUS Express	Paclitaxel (100 μg cm^{-2})	Poly(styrene-*b*-isobutylene-*b*-styrene)	16	<10	SS	132	1.245	11.9/3.8
TAXUS Liberté	Paclitaxel (100 μg cm^{-2})	Poly(styrene-*b*-isobutylene-*b*-styrene)	16	<10	SS	97	1.219	13.7/4.4
Endeavor	Zotarolimus (100 μg cm^{-2})	Phosphorylcholine	4.1	95[b]	CoCr	91	1.130	19.8/6.3
Resolute	Zotarolimus (100 μg cm^{-2})	BioLinx (C10, C19, polyvinyl pyrrolidinone	4.1	85[c]	CoCr	91	1.130	19.8/6.3
Xience V	Everolimus (100 μg cm^{-2})	PVDF+HFP+PBMA	7.6	80	CoCr	81	1.055	12.6/4.0

SS, stainless steel; CoCr, cobalt–chromium; PVDF-HFP, poly vinylidene fluoride *co*-hexafluoropropylene; PBMA, poly-*n*-butyl methacrylate.
[a]Based on a 3-mm stent.
[b]Drug release at 14 days.
[c]Drug released at 60 days.

Table 3 Comparison of the composition of different stent platform alloys

	Elemental composition (wt%)			
	316L stainless steel	Platinum–chromium alloy	L605 cobalt–chromium alloy	MP35N cobalt–chromium alloy
Iron	64	37	3.0[a]	1.0[a]
Platinum		33		
Cobalt			52	34
Chromium	18	18	20	20
Nickel	14	9	10	35
Tungsten			15	
Molybdenum	2.6	2.6		9.75
Manganese	2.0[a]	0.05[a]	1.5	0.15[a]
Titanium				1.0[a]

[a]Maximum.

Irrespective of clinical situation, when compared with BMS, the use of SES results in significant reductions in angiographic in-stent late loss; in-stent angiographic stenosis; and repeat revascularization at both short- and long-term 5-year follow-up, with results consistent across numerous different patient and lesion types. Furthermore, meta-analyses of patient data from the initial approval trials reaffirm the sustained advantage of SES over BMS in terms of reduced repeat revascularization, together with comparable rates of death and MI at long-term follow-up.[46–50]

Table 4 Comparison of the radio-opacity, strut thickness, radial strength, acute recoil, and conformability of different stent platforms

Stent	*Endeavor*	*Xience V*	*Cypher*	*TAXUS Liberté*	*TAXUS Element*
Stent platform	Cobalt–chromium	Cobalt–chromium	Stainless steel	Stainless steel	Platinum–chromium
Strut thickness (μm)	91	81	140	96	81
Radio-opacity ($g\,cm^{-3}$)		9.1		8.0	9.9
Radial strength[a] ($N\,mm^{-1}$)	0.14	0.11	0.17	0.24	0.26
Recoil[b] (% recoil)	5.1	4.6	3.4	2.8	3.0
Conformability[c] ($N\,mm^{-1}$)	0.06	0.30	1.00	0.09	0.04

[a]Amount of radial force required to reduce the diameter of a deployed stent (higher values preferred).
[b]Percentage of the stent diameter which decreases after balloon deflation (lower values preferred).
[c]Measure of the ability of the stent to naturally conform to the vessel (lower values preferred).

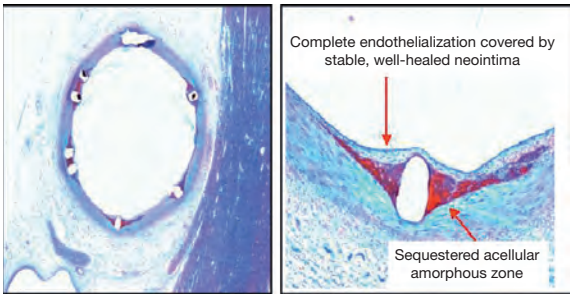

Figure 7 Sirolimus-eluting stent implantation in a porcine model demonstrating complete endothelialization of the stent struts without the development of significant neointimal hyperplasia.

Registries have also evaluated the performance of the Cypher stent in a 'real-world' setting. The first of these registries was the single-center RESEARCH (Rapamycin Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry, which enrolled 508 consecutive patients, who were treated with the Cypher SES irrespective of lesion complexity. Running concurrently with the RESEARCH registry was the multicenter ARTS-II (Arterial Revascularization Therapies Study) registry, which assessed the Cypher stent in 607 patients with two and three vessel CAD. Results from both registries at short and long-term follow-up, which now extends to 4 and 5 years for the respective RESEARCH and ARTS-II registries, mirror those from other registries, and the aforementioned randomized studies and meta-analyses, by continuing to demonstrate significantly lower rates of MACE and TLR following the use of the Cypher SES compared to historical BMS controls.[51–55]

6.627.4.2. Paclitaxel-Eluting Stent

Paclitaxel is a highly lipophilic diterpenoid compound that was first discovered in the pacific yew tree *Taxus brevifolia* in 1963 (**Figure 6**). This agent shifts the cytoskeletal equilibrium toward assembly, thereby inhibiting cell division in the G0/G1 and G2/M phases, which leads to reduced vascular cell proliferation, cell migration, cytokine and growth factor release and activity, interference with secretory processes, antiangiogenic effects, and impaired signal transduction.[56] At high doses, paclitaxel produces mitotic arrest in the G2/M phases of the cell cycle and promotes apoptosis. Conversely, at the low doses that are used on the paclitaxel-eluting stent (PES), paclitaxel affects the G0-G1 and G1-S phases, resulting in cytostasis without cell death. The first TAXUS PES (Boston Scientific, Natick, MA) consisted of paclitaxel contained within a polyolefin derivative biostable polymer coated on the stainless steel NIR platform. A slow-release (SR) formulation with an 18-μm thick coat, a moderate release (MR) with a 7-μm coat, and a fast release with 4-μm coat shed 8, 22, and 50% of the paclitaxel within 30 days, respectively. The difference in release was achieved by changing the polymer to drug ratio while maintaining the same paclitaxel concentration ($1\,\mu g\,mm^{-2}$).[57] The TAXUS PES has been evaluated in the TAXUS series of trials which have enrolled different patient and lesion types:

- The TAXUS I trial, a FIM phase I feasibility study with 61 randomized patients, reported a 3% MACE rate versus 10% in BMS at 1 year. Patients in the PES group had no TLR or binary stenosis, proving that paclitaxel effectively inhibited neointinal proliferation.[58]
- The TAXUS II study randomized 536 patients to treatment with BMS or SR PES, and BMS or MR PES. The reduction in percentage neointimal hyperplasia as measured by IVUS at 6 months was 7.8% for SR and 7.8% for MR versus 23.2% and 20.5% for control BMS.[59] These results provided the foundation for the sustained reduction in TLR of 4.5 and 10.3% for the MR PES and SR PES, respectively, (BMS 18.4%, BMS vs. PES $p < 0.001$) out to 5 years.[60] Of note, the MR formulation which was not subsequently used for

commercialization showed a better antirestenotic effect than the SR formulation at 5 years.

- TAXUS III tested the fast release PES in 28 patients with in-stent restenosis. At 6 months, the in-stent late loss was 0.54 mm with a neointimal hyperplasia volume of 20.3 mm^3, and a subsequent MACE rate was 29%. Overall results suggested that PES was a potentially efficacious treatment in those with in-stent restenosis.[61]
- The platform of the PES was changed from the NIR platform to less rigid Express platform (**Table 2**) and this combination was studied in the TAXUS IV study, which randomized 1326 patients with noncomplex CAD to treatment with the TAXUS Express stent or Express BMS. TVR at 9 months was significantly lower in the PES group (12.1% vs. 4.7%; $p < 0.0001$) and this advantage was maintained through to 5 years (27.4% vs. 16.9%; $p < 0.0001$), despite comparable annual TVR rates for BMS and PES between years 1 and 5 (4.1% per year vs. 3.3% per year, respectively, $p = 0.16$).[62,63]
- TAXUS V randomized 1156 patients, over half of whom had complex coronary lesions not studied in earlier PES trials, to treatment with PES ($n = 557$) and BMS ($n = 579$). Consistent with earlier studies, use of PES lead to significantly lower rates of angiographic stenosis, TLR, and TVR at 9 months, with comparable rates of death, MI, and ST. The benefit in favor of PES was maintained out to 5-year follow-up; however, PES was also associated with higher rates of MI (9.3% vs. 5.6%, $p < 0.05$) and definite/probable ST (2.4% vs. 1.5%, $p < 0.05$).[64,65]
- TAXUS VI also randomized 446 patients with long complex lesions to treatment with either PES or the Express BMS. At 9-month follow-up, use of PES led to significantly lower rates of binary stenosis, TLR, and TVR, while the overall MACE rate was similar. Subsequent 5-year follow-up demonstrated the sustained antirestenotic effect of PES on TLR (14.6% vs. 21.4%, $p = 0.03$); however, a significantly higher rate of non-TLR was also seen in the PES group (10.9% vs. 5.1%, $p = 0.03$). Rates of ST and MACE were similar.[66,67]

In a fashion similar to the SES, the TAXUS PES has been assessed in an unrestricted single-center registry, which used the PES as the default stent for all PCI in 576 consecutive 'real-world' patients. Two-year results from the T-SEARCH registry (Taxus Stent Evaluated at Rotterdam Cardiology Hospital) demonstrate similar efficacy in terms of suppression of neointimal growth and reduction of restenosis when compared to historical controls treated with SES.[68,69] In addition, patient level meta-analysis of the initial PES approval trials has confirmed the comparable safety and superior efficacy of PES, in relation to BMS, up to 4-year follow-up.[49,50]

6.627.4.2.1. TAXUS express versus TAXUS liberté

The TAXUS PES Express stent was the first PES approved by the FDA; however, it was subsequently replaced by the TAXUS PES Liberté stent, which was designed to be more deliverable and conformable, and to provide a more homogenous drug distribution.[70] Both stents utilized an identical polymer, dose of paclitaxel and release kinetics; however, the Liberté stent had a more uniform cell geometry allowing more enhanced and uniform drug delivery; thinner struts (97 vs. 132 μm); a smaller profile; and different stents designs depending on stent diameter (two cell stent for diameters 2.25–2.5 mm and three cell stent for diameter >2.75 mm) (**Tables 2–4**).

The superiority of the newer Liberté stent was confirmed by the multicenter noninferiority TAXUS ATLAS clinical trial. The study enrolled 871 patients treated with the TAXUS Liberté stent, who were compared to historical controls treated with the TAXUS Express-SR stent from the TAXUS IV and V trials.[70] In spite of similar inclusion criteria, patients with the Liberté stent received treatment for significantly more complex baseline lesions, however,the primary endpoint of 9-month TVR achieved the prespecified criteria for noninferiority (Express 7.0% vs. Liberté 8.0%, $p = 0.049$). There were no significant differences in other clinical outcomes.

Two subsequent studies, the TAXUS ATLAS Small Vessels study and the TAXUS ATLAS Long Lesions study, have also confirmed improved outcomes up to 3-year follow-up with the newer Liberté stent, specifically in patients with lesions treated with a single 2.25 mm TAXUS Express stent, and in patients with lesions 26–34 mm in length treated with a single 38 mm TAXUS Express stent.[71,72]

6.627.5. Benefits of DES

The previous discussion highlights the clear benefit DESs have over BMS in terms of reducing the risk of restenosis, which has been demonstrated in multiple randomized trials, and reaffirmed by meta-analyses. Results from the largest meta-analysis thus far, which included over 18 000 patients from 38 DES trials, indicated a reduction in TLR of 70% ($p < 0.0001$) with the use of SES, and 58% ($p < 0.001$) with the use of PES, when compared to BMS, which is up to 4-year follow-up.[49] This corresponded to a number needed to treat to prevent a single revascularization of only seven and eight patients for SES and PES, respectively. Encouragingly, consistent results have also been demonstrated in numerous other meta-analyses.[46–48,50] Importantly, these impressive results are not only confined to randomized studies which enrolled patients treated for 'on-label' indications, but have also been seen in registries, and randomized controlled trials which have included patients receiving DES for complex or 'off-label' indications.[52,73,74]

6.627.6. Risks of DES

- Restenosis

Despite the marked reduction in restenosis rates with the use of DES as compared to the use of POBA and BMS, clinically driven TLR remains common. These events which hinder the efficacy profile of the stents are even more common in real-world practice as has been consistently shown by registry data. Stenting in patients with diabetes, in those lesions at ostial locations, in small vessels, in lesions requiring long stented segments or stent overlap, and in the treatment of in-stent restenosis has been associated with a higher risk of repeat TVR. Restenosis in these high risk situations cannot be attributed to excessive neointimal proliferation alone, and in fact, failure of stenting in these situations is more likely to

be due to a combination of factors such as operator chosen stenting strategy, patient and lesion characteristics, as well as physical characteristics of the stent, including scaffolding/recoil. Inadequate stent expansion, incomplete apposition, strut fracture, geographical miss, and lesion calcification may all contribute to vessel recoil and inadequate drug elution to the vessel wall.[75,76]

- Stent thrombosis

ST is not unique to DES and in fact, as mentioned earlier, it has been a major problem since the first BMS were implanted. Although rare, it is a devastating, unpredictable event which carries significant morbidity and mortality.[77,78] The partial or complete clogging of the artery with thrombus results in the commonest mode of presentation, being symptoms typical of an acute coronary syndrome including ST-elevation MI.

In the DES era, concerns over the possible increased risk of ST compared to the earlier rates experienced with BMS led to collaborative efforts to investigate this issue. To assist in this assessment, large-scale registries and meta-analysis were performed, the majority of which employed the standardized definitions proposed by the Academic Research Consortium,[79] and reported no overall difference in rates of ST between DES and BMS. Of note, division of ST according to its timing indicated comparable rates of early (<30 days), and late (30 days to 1 year) ST; however, DESs were associated with significantly higher rates of very late (>1 year) ST (**Table 5**).[47–50,80]

The annual risk of ST seen in post marketing surveillance registries was ~0.2%, rising to 0.5% in trials of multivessel PCI.[81–84] Of importance, rates of ST at the different time points post DES implantation vary significantly as exemplified by the Dutch Stent registry (437/21009 patients with documented ST) where 32.0%, 41.2%, 13.3%, and 13.5% (146) of ST events occurred acutely, subacutely, early, and late.[85] Furthermore, registry data from the Rotterdam–Bern group (8146 patients), the SCAAR registry (21 717 patients), and from Pinto Slottow's *et al.* registry (8000 patients) have all indicated that the risk of very late ST persists at an annual rate of between 0.36% and 0.6% per year out to at least 5 years after DES implantation.[86–91] In addition, the results at 2-year follow-up from both the ARRIVE and STENT registry also suggest that the risk of ST is higher in those patients treated with DES for 'off-label' compared to 'on-label' indications.[92,93]

Numerous potential causes have been implicated as a risk factor for a ST event.[85,86,91,94] The possible increased thrombogenicity of DES as compared to BMS was attributed to lack of vessel endothelialization, vascular toxicity, and hypersensitivity reactions. A recent small scale study suggested stent malapposition as a more frequent finding in DES, whereas disease progression with neointimal rupture was more common in BMS.[95] Procedure related factors, such as stent under sizing, lesion length >28 mm, dissection, multiple stent implantation, stenting at bifurcations, calcification, and small vessel diameter, and most notably early cessation of DAPT, have been associated with development of early/late, but not very late, ST.[85,94] Renal failure and previous brachytherapy seem to be more important in very late ST.

Currently, efforts are underway to reduce the risk of ST, utilizing the vast acquired knowledge of factors which have been implicated in its occurrence. As discussed in the rest of this chapter, the development of newer stents with new stent platforms, new stent designs, and safer drug release mechanisms aims to decrease the inherent thrombogenicity of the stent itself. Coupled with these changes, are developments in imaging techniques that help better identify features implicated in precipitating ST, such as malapposition and dissections in the acute phase, thereby allowing immediate correction, which could potentially help in reducing ST events. Finally with respect to DAPT, investigations are underway to establish the optimal duration of DAPT, the full potential of new antiplatelet agents such as prasugrel and ticagrelor, and the optimal treatment of patients with antiplatelet resistance.

6.627.7. Second Generation DES

The previously discussed safety concerns that emerged with the first generation DES prompted the development of newer coronary stents, which utilized more biocompatible polymers, aimed more specifically at mimicking the endothelial lining in order to prevent thrombotic complications. In addition, these newer stents moved away from stent platforms using 316L stainless steel, and instead used cobalt–chromium, an alloy with improved radio-opacity and superior radial strength, thereby allowing thinner stent struts (**Tables 2–4**). Notably, previous studies of bare-metal and drug-eluting stainless steel

Table 5 Rates of overall, early, late, and very late stent thrombosis from recent meta-analyses comparing drug-eluting stents to bare-metal stents

Reference	*Stent (number of patients)*		*Longest follow-up (years)*	*Overall ST (DES vs. BMS)*	*Early ST (DES vs. BMS)*	*Late ST (DES vs. BMS)*	*Very late ST (DES vs. BMS)*
ST defined according to Academic Research Consortium definitions							
Spaudling *et al.*[48]	SES (878)	BMS (870)	4	3.6% vs. 3.3%	0.5% vs. 0.5%	0.3% vs. 1.3%[a]	2.8% vs. 1.7%
Stettler *et al.*[49]	SES (4643)	BMS (4003)	4	HR 1.00	HR 1.02	HR 1.14	HR 1.43
Stettler *et al.*[49]	PES (4327)	BMS (4003)	4	HR 1.38	HR 0.95	HR 1.61	HR 3.57
Mauri *et al.*[47]	PES (1400)	BMS (1397)	4	3.2% vs. 3.5%	0.5% vs. 0.5%	0.9% vs. 0.9%	1.8% vs. 2.1%
ST defined according to protocol							
Stone *et al.*[50]	SES (878)	BMS (870)	4	1.2% vs. 0.6%	0.5% vs. 0.1%	0.1% vs. 0.5%	0.6% vs. 0.0%[a]
Kastrati *et al.*[46]	SES (2486)	BMS (2472)	5	HR 1.09	–	–	0.6% vs. 0.05%[a]
Stone *et al.*[50]	PES (1755)	BMS (1758)	4	1.3% vs. 0.9%	0.5% vs. 0.6%	0.2% vs. 0.1%	0.7% vs. 0.2%[a]

Difference nonsignificant unless indicated. BMS, bare-metal stent; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; ST, stent thrombosis; HR, hazard ratio.
[a] $p < 0.05$.

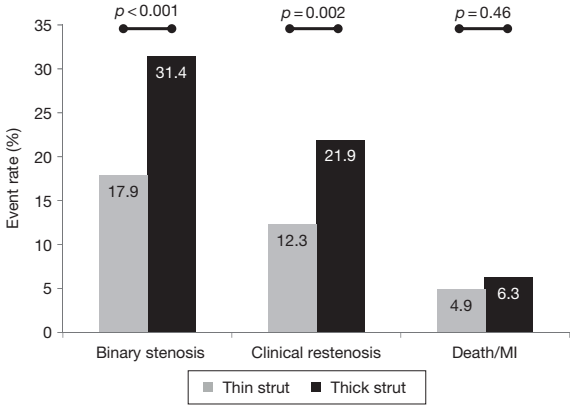

Figure 8 The rate of binary restenosis (diameter stenosis ≥50%) at 6-month follow-up together with the rate of clinical restenosis and death/myocardial infarction at 1-year follow-up among patients treated with bare-metal stents with thin or thick struts in the ISAR-STEREO-2 trial. Adapted from Pache, J.; Kastrati, A., Mehilli, J.; *et al*. *J. Am. Coll. Cardiol*. **2003**, *41*, 1283–1288.

stents have indicated that stent strut thickness has a significant adverse impact on long-term rates of restenosis and clinical outcomes (Figure 8).[70–72,96,97] Therefore, reducing strut thickness not only has distinct potential advantages with respect to outcomes, but also allows devices to be of lower profile, improving overall stent deliverability. The second generation DES comprise the Endeavor (Medtronic, Santa Rosa, CA) zotarolimus-eluting stent (E-ZES), the Resolute (Medtronic) zotarolimus-eluting stent (R-ZES) and the XIENCE V everolimus-eluting stent as described below.

6.627.7.1. Zotarolimus-Eluting Stents

- Endeavor stent (Medtronic, Santa Rosa, CA)

This cobalt–chromium stent has a strut thickness of 91 μm, and is loaded with 100 μg cm^2 of the macrocylic lactone zotarolimus. The drug is released in a rapid fashion such that 95% is eluted within 14-days of implantation, release of which is facilitated by a 4.1-μm thick permanent 'biomimetic' phosphorylcholine polymer which is biostatic and biocompatible, being a natural component of the cell membrane (Tables 2–4). The superior biocompatibility of the polymer is suggested by studies which demonstrate less inflammation with this polymer compared to the methacrylate polymer found on the Cypher SES; in addition, animal and *in vivo* studies using angioscopy and optical coherence tomography (OCT) both demonstrate a greater endothelial coverage of struts, potentially as a result of less inflammation, with E-ZES compared to SES, and PES (Figure 9).[98–101]

The first clinical evaluation of the stent took place in the 100 patient single-arm ENDEAVOR I study. At 12 months, in-stent late loss and binary restenosis were 0.61 mm and 5.4%, respectively. Clinic event rates were low, with two TLRs, one MI, and one definite/probable ST at 1 year, and only one further TLR and no additional MIs or ST events were reported up to 5-year follow-up.[102,103] More extensive assessment of E-ZES has taken place in randomized comparisons with BMS, and first generation DES as described in Sections 6.627.7.3 and 232.7.4, respectively.

- Resolute ZES (Medtronic, Santa Rosa, CA)

The Resolute ZES (R-ZES) uses the same stent platform and dose of antiproliferative agent as that found on the Endeavor stent; however, zotarolimus release is controlled by the BioLinx polymer – a blend of three different polymers: the hydrophobic C10 polymer to control drug release; the biocompatible and hydrophilic C19 polymer; and polyvinyl pyrrolidone to allow an early burst of drug release (Table 2 and Figure 10).[104] The polymer prolongs drug release, such that at least 85% of the zotarolimus is released within 60 days, with the remainder being released within 180 days. The prolonged drug elution is aimed at matching the delayed healing times seen in complex lesions.

The first assessment of the R-ZES took place in the 139 patient, single-arm RESOLUTE study. At 9-month follow-up, angiographic in-stent late loss was 0.22 mm, which was notably less than the ≈0.6 mm consistently seen with the E-ZES. Rates of MACE, TLR, and any definite/probable ST were 8.6%, 0.7%, and 0.0%, respectively at 12-month follow-up, and 11.6%, 1.6%, and 0.0%, respectively at 3-year follow-up.[105–107] The R-ZES has also been assessed in a large randomized study as described in Section 6.627.7.5.

6.627.7.2. Everolimus-Eluting Stent

- XIENCE V

The cobalt–chromium EES stent has a strut thickness of 81 μm, and is coated with a 7.6-μm thick, nonerodable, copolymer of poly vinylidene fluoride *co*-hexafluoropropylene (PVDF-HFP), and poly *n*-butyl methacrylate (PBMA) (Tables 2–4, and Figure 11). The polymer facilitates the elution of the sirolimus analog, everolimus over 120 days. Of note,

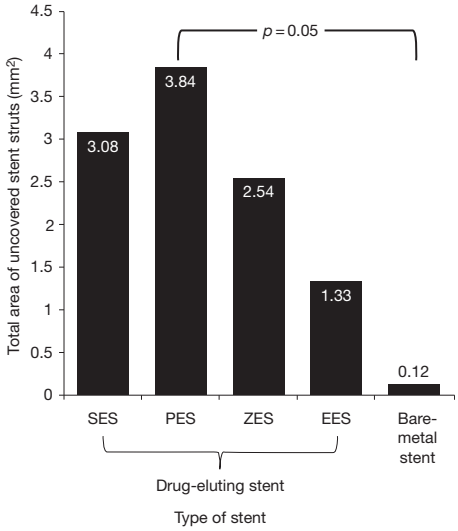

Figure 9 The difference in total area of stent struts that have not been endothelialized according to stent type at 1 month in a rabbit model. SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; ZES, Endeavor zotarolimus-eluting stent; EES, everolimus-eluting stent. Adapted from Joner, M.; Nakazawa, G.; Finn, A. V.; *et al. J. Am. Coll. Cardiol*. **2008**, *52*, 333–342.

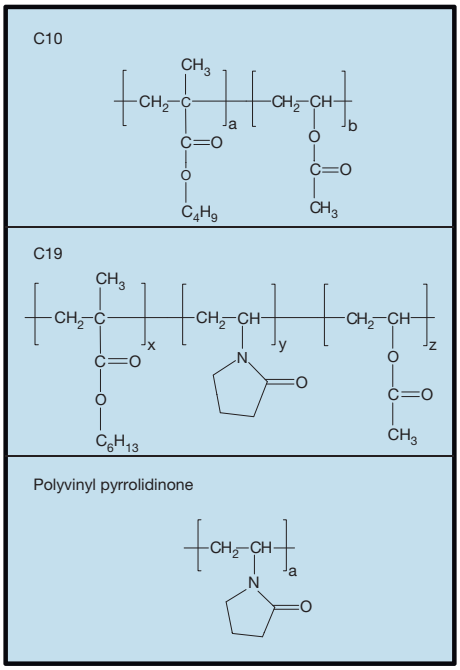

Figure 10 The chemical structure of the three components of the BioLinx polymer on the Endeavor Resolute stent. The hydrophobic C10 polymer is based on hydrophobic butyl methacrylate to provide adequate hydrophobicity for zotarolimus. The hydrophilic C19 polymer is manufactured from a mixture of hydrophobic hexyl methacrylate, and hydrophilic vinyl pyrrolidinone and vinyl acetate monomers, to provide enhanced biocompatibility. The hydrophilic polyvinyl pyrrolidinone increases the initial drug burst and enhances biocompatibility.

preclinical studies have demonstrated more rapid endothelialization in rabbit iliac arteries implanted with an EES when compared to that with SES, PES, and E-ZES (**Figure 9**).[99]

The FUTURE I[108,109] and FUTURE II[110] studies were the first to demonstrate the feasibility of using everolimus on a DES, and subsequent trials, as indicated below, include randomized studies comparing EES with BMS, PES, and R-ZES.

- Xience PRIME™ (Abbott Vascular, Santa Clara, CA)

The Xience PRIME EES, which represents the newest development of the Xience® V stent, has recently gained regulatory approval in Europe. This modified EES has a CoCr platform; however, this is mounted on a new enhanced stent delivery system that enables the stent to be more flexible and deliverable. Furthermore, the stent balloon has higher rate burst pressures, and shorter balloon tapers to minimize the risk of edge dissections. The stent is being evaluated in the prospective, multicenter, nonrandomized SPIRIT PRIME study in 500 patients at 75 hospital centers, with the aim of gaining US FDA approval.

6.627.7.3. Second Generation DES Versus BMS

The ENDEAVOR II and SPIRIT FIRST trials were the first respective randomized evaluations of E-ZES and EES, with BMS as the comparator. The ENDEAVOR II trial enrolled 1197 patients (E-ZES = 598, BMS = 599) and demonstrated significantly lower rates of in-stent late loss (0.61 vs. 1.03 mm, $p < 0.001$),

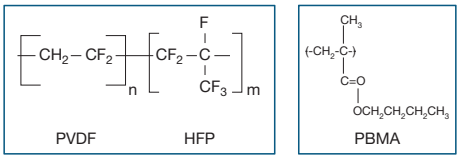

Figure 11 The structure of the Xience V everolimus-eluting stent polymer which is a copolymer of poly vinylidene fluoride *co*-hexafluoropropylene (PVDF-HFP), and poly *n*-butyl methacrylate (PBMA).

binary in-stent restenosis (9.4% vs. 33.5%, $p < 0.001$), TLR (4.6% vs. 11.8%, $p < 0.001$), and target vessel failure (TVF; a composite of cardiac death, MI attributable to the target vessel, and clinically driven TLR) (7.9% vs. 15.1%, $p < 0.001$) at 9-month follow-up, with additional clinical follow-up at 5 years indicating a sustained benefit in favor of E-ZES with respect to TLR and TVF.[111,112] Mortality and rates of MI and ST were comparable at all time points. Of note, unlike long-term

follow-up of the SIRIUS and TAXUS II study,[33,60] there was no reduction with time in the absolute difference in TLR between E-ZES and BMS (Δ7.2% at 1 year, Δ8.8% at 5 years).

The smaller SPIRIT FIRST study enrolled 56 patients (EES = 27, BMS = 29) and demonstrated superior performance of EES at 6-month and 5-year follow-up with respect to similar angiographic, and clinical endpoints as assessed in the ENDEAVOR II study.[113,114]

6.627.7.4. Second Generation DES Versus First Generation DES

After establishing their superiority over BMS, both second generation DESs have been compared to the first generation DES. While E-ZES has been compared in different randomized trials to both PES and SES, EES has only been compared to PES. Overall results with E-ZES have been inconsistent, while a clear benefit in favor of EES has been shown in its comparison with PES.

- E-ZES versus SES

The comparison of E-ZES and SES has taken place in the randomized ENDEAVOR III study which enrolled 436 patients (E-ZES = 323 and SES = 113) and the SORT-OUT III study which randomized 2332 patients (E-ZES ($n = 1162$) and SES ($n = 1170$)).[115–117] At short-term follow-up, results of both studies suggested superiority of SES. Notably, the ENDEAVOR III study failed to reach its noninferiority primary endpoint of in-stent late loss at 8-month follow-up (E-ZES 0.34 mm vs. SES 0.13 mm, $p < 0.001$); however, despite this, rates of TLR, mortality and TVF were similar in the stent groups. In contrast, in the SORT-OUT III study at both 9- and 18-month follow-up, significant differences in favor of SES were observed with respect to MI, TLR, and ST. Results at long-term follow-up of the ENDEAVOR III study suggest a more sustained antiproliferative effect with E-ZES compared with SES. Specifically at 5 years, the absolute difference in TLR between E-ZES and SES was 1.6% (E-ZES 8.1% vs. SES 6.5%) compared to an absolute difference at 9 months of 2.8%. Rates of ST remained similar in both groups throughout follow-up, although neither study was powered for this endpoint.

- E-ZES versus PES

The ENDEAVOR IV study randomized 1548 patients to E-ZES ($n = 773$) and PES ($n = 775$).[118] The study demonstrated noninferiority of E-ZES compared to PES with respect to the primary endpoint of TVF (E-ZES 6.6% vs. PES 7.2%); no significant differences were noted in other clinical endpoints at 1-year, with results maintained through to 3-year follow-up.[119] Similar to the ENDEAVOR III study, there was a reduction with time in the absolute difference in TLR between E-ZES and PES from 1.3% at 1 year to 0.5% at 3 years. Angiographic follow-up at 8 months demonstrated an in-stent late loss of 0.67 and 0.42 mm for E-ZES and PES, respectively ($p < 0.001$).

In summary, the comparison of E-ZES with first generation DES have shown similar results, with significantly inferior values for late loss observed on angiographic follow-up at between 6 and 8 months; however, this has not translated into any significant differences in clinical endpoints. Moreover, at long-term follow-up a reduction in the absolute difference between E-ZES and the comparator stent has been seen, which may suggest absence of the 'late catch-up' phenomena with E-ZES.

With respect to ST, no study has been adequately powered to detect differences, and consequently the results of the PROTECT study, anticipated in 2011, are eagerly awaited. This study has randomized 8800 'all-comers' patients to treatment with either the E-ZES or SES, and will report a primary endpoint of definite/probable ST at 3-year follow-up.[120]

- EES versus PES

EES has been compared to PES in several randomized studies which have enrolled increasingly complex patients ranging from those with up to two *de novo* lesions in the SPIRIT II study,[121–125] to the unrestricted all-comers population in the COMPARE study.[126] Irrespective of patient complexity or follow-up period, angiographic and clinical outcomes have been superior in those treated with EES. Specifically, in the SPIRIT II and SPIRIT III study in-stent late loss at 6 and 8 months, respectively, was significantly lower with EES.[125,127] Longer angiographic follow-up has only been performed in the SPIRIT II study, and this demonstrated evidence of delayed late loss with EES such that there was no longer a significant difference in in-stent late loss at 2 years.[121] Nevertheless, despite this observation, clinical outcomes at 3- and 4-year follow-up in the SPIRIT II study remained consistent with those seen at 6-month and 1-year follow-up, with numerically lower rates of cardiac death, MI, TLR, and overall MACE with EES. Similarly, at 3-year follow-up in the SPIRIT III study, treatment with EES led to significantly lower rates of TVF, target lesion failure, and MACE.[128] More extensive assessment of EES has taken place in the SPIRIT IV, which randomized 3690 patients (EES = 2458, PES = 1229), and represents the largest randomized trial comparing two DESs, and the COMPARE study, which recruited 1800 patients (EES = 897, PES = 903) and was the first randomized all-comers trial of the EES.[126,129] Both studies demonstrated significantly superior efficacy and safety with EES compared to PES. In addition, while nonsignificantly lower rates of ST have been observed in the SPIRIT II and III studies, the SPIRIT IV and COMPARE studies were the first to demonstrate a significant reduction in ST between two DES. At 12-month follow-up, rates of definite/probable ST for EES and PES were 0.29% versus 1.06% ($p = 0.003$), and 0.7% versus 2.6% ($p = 0.002$) in the SPIRIT IV and COMPARE studies, respectively.

6.627.7.5. Second Generation DES Versus Second Generation DES

The only data comparing two second generation DES come from the RESOLUTE All-Comers Trial. This study, which randomized 2300 patients to treatment with the R-ZES or EES, had an all-comers design, such that one-third of the population enrolled presented with ST-elevation MI, and two-thirds had at least one off-label indication.[130] The study achieved its prespecified criterion for noninferiority of the primary endpoint of target lesion failure (a composite of cardiac death, MI attributable to the target vessel, and clinically driven TLR) at 12-month follow-up (R-ZES 8.2% vs. EES 8.3%, $p_{\text{noninferiorty}} < 0.001$). In addition, the study also achieved its powered angiographic

endpoint of percent diameter stenosis at 13-month follow-up (R-ZES 21.7% vs. EES 19.8%, $p_{\text{noninferiorty}} = 0.04$). All other clinical endpoints were similar in both groups, including rates of ST, which were reassuringly low despite the complexity of the patient population.

6.627.8. New Drug-Eluting Stents

There is no doubt that the introduction of the DES revolutionized the practice of interventional cardiology. The first generation DESs undeniably offered distinct advantages over their BMS predecessors; however, safety concerns emerged with their use in the more diverse patient populations encountered in routine clinical practice. These concerns subsequently prompted development of second generation DES which had more biocompatible polymers, and results have so far been impressive, albeit at only medium-term follow-up.[122,131] The problem of ST persists however, and focus has now turned to developing newer DESs which utilize newer types of polymer. Of note, current first and second generation DESs use nonerodable polymers, which remain exposed to the coronary artery environment long after their useful function has been served, and consequently have been implicated in causing persistent arterial wall inflammation, and delayed vascular healing, both of which may play a role in precipitating ST and delayed restenosis.[99,132–135]

Advances in polymer technology have led to the development of DESs which have polymers that biodegrade into inert monomers over 6–9 months, or DESs which are completely polymer free. A final extension to these new developments is the concept of completely biodegradable stents which are discussed in.

A robust method of classifying this heterogeneous group of new stents, many of which are still undergoing preclinical and/or early FIM studies, has not yet been determined, but for simplicity, in the following discussion they are grouped according to the type of polymer. Of note, those stents utilizing new stent platforms such as platinum–chromium and nitinol are covered separately.

6.627.8.1. DES with Biodegradable Polymers

This represents the largest group of new DESs, with numerous devices undergoing current clinical evaluation, and some already commercially available in Europe. In theory, immediately after implantation these devices function similar to conventional DES; however, after polymer breakdown, they speculatively may offer the safety benefits of BMS. Short-term results from these stents have been encouraging; however, in the absence of long-term data it is not possible to definitively state that this technology will lead to improved clinical outcomes, most notably with respect to improved safety.

There are many challenges remaining for this new polymer technology, which include among others, establishing the optimal biocompatibility, composition, formulation, and degradation time of the polymer. In addition, attention must be paid to the pharmacokinetics of the antiproliferative agent released by the degradation of the polymer, and the variation in polymer degradation time which can be affected by production factors such as the use of long polymer chains, decreased polymer hydrophobicity, and greater polymer crystalinity, together with physical and biological environmental factors.[136] Evidence indicates that polymer breakdown can be associated with a significant inflammatory reaction which at times can create an acidic environment; moreover, complications may also occur as a result of a persistent immune response to monomer breakdown products.[137] These uncertainties reiterate the need for continued research, with clinical outcomes assessed at long-term follow-up.

The most prominent DESs with biodegradable polymers include those eluting biolimus A9, sirolimus, and paclitaxel, as described below.

6.627.8.1.1. Biolimus A9-eluting DES with biodegradable polymers

The most widely studied DESs with biodegradable polymers elute the highly lipophillic macrocyclic lactone biolimus A9, which is an analog of sirolimus that inhibits T cell and smooth muscle cell proliferation. The main difference between biolimus A9 and rapamycin is replacement of hydrogen by alkoxy-alkyl group at 40-O position, increasing its lipophilicity (**Figure 4**). The drug has been combined on several different stent platforms with an abluminal poly-lactide polymer, which biodegrades completely within 6–9 months of stent implantation (**Figure 12**). The abluminal location of the drug/polymer matrix is aimed at further improving overall safety, by allowing more targeted tissue release, and reducing systemic exposure.

- Biomatrix™ stent (Biosensors, Morges, Switzerland)

The stainless steel BioMatrix Flex™ stent (**Figure 12**) was initially evaluated in the 120 patient FIM STEALTH I trial which randomized patients to the biolimus-eluting stent (BES) or a BMS. At 6 months, angiographic follow-up rates of in-stent late lumen loss and angiographic stenosis were significantly lower with BES.[138] Results at 5-year follow-up from a subgroup of 32 patients demonstrate low rates of overall MACE, and importantly no episodes of ST.[139]

More recent evaluation took place in the all-comers noninferiority LEADERS study, which randomized 1707 patients to treatment with BioMatrix BES or the Cypher SES. At 9-month follow-up, BES was shown to be noninferior with respect to the primary endpoint of MACE, a composite of cardiac death, MI, and ischemia driven TVR (9% vs. 11%, $p_{\text{noninferiority}} = 0.003$, $p_{\text{superiority}} = 0.39$),[140] with results subsequently maintained at 12- and 24-month follow-up.[141,142] The stent's PLA polymer is expected to have completely biodegraded by 9 months (**Figure 12**), and therefore, even though the study is not adequately powered to detect differences in ST events, it is promising to observe the occurrence of less very late ST events (>1 year) with BES (0.2% vs. 0.5%).[142] Further data in support of the biodegradable polymer concept were obtained in an OCT substudy, which demonstrated a higher rate of near complete (>95%) strut coverage with BES when compared to the Cypher SES at 9-month follow-up (89.3% vs. 63.3%, $p = 0.03$).[143]

- Nobori™ stent (Terumo, Japan)

The Nobori™ stent is very similar to the BioMatrix Flex stent, utilizing the same polymer, antiproliferative agent, and stent platform; however, the delivery system, delivery balloon,

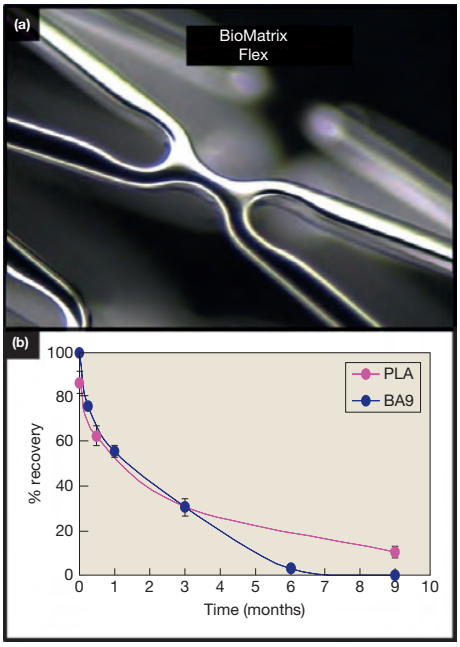

Figure 12 The BioMatrix Flex stent. (a) The stainless steel BioMatrix Flex stent. (b) The elution pattern of Biolimus A9 (BA9) and the corresponding biodegradation pattern of the poly-lactic acid (PLA) polymer.

and the stent coating process are different. In the NOBORI CORE study, which randomized 99 patients to treatment with the Nobori BES or the Cypher SES, there was no significant difference in 9-month angiographic in-stent late lumen loss (0.10 vs. 0.12 mm, $p = 0.66$).[144]

In the larger Nobori I study, 243 patients were randomized to treatment with either the Nobori™ stent ($n = 153$) or the TAXUS PES stent ($n = 90$). At 9 months, the Nobori stent was shown to be noninferior, and subsequently superior to the PES with respect to late loss (0.11 vs. 0.32 mm, $p_{\text{noninferiority}} < 0.001$, $p_{\text{superiority}} = 0.001$). In addition, the rate of ARC defined ST at 9-month follow-up was also lower with the Nobori stent (0.0% vs. 2.2%).[145] Encouragingly no episodes of very late ST have been reported in any study assessing the Nobori stent, which in total have enrolled over 3000 patients. Clinical evaluation continues in large-scale randomized trials comparing the stent to the EES in the COMPARE 2 ($n = 2700$ patients) and BASKET PROVE 2 ($n = 2400$ patients) studies, and to the Cypher Select SES in SORT-OUT IV study ($n = 2400$ patients).[146]

- Axxess™ stent (Devax Inc., Lake Forest, CA, USA)

The Axxess stent is a BES which is made of nitinol and designed specifically for bifurcation lesions. It is described in Section 6.627.8.4.2.

6.627.8.1.2. Sirolimus-eluting DES with biodegradable polymers

- NEVO™ Stent (Cordis, Warren, NJ, USA)

The NEVO™ stent is an open-cell, cobalt–chromium stent, with a PLGA biodegradable polymer which facilitates elution of sirolimus. The stent is unique in its design as the polymer and sirolimus are contained within reservoirs, which eliminate the need for a surface polymer coating, and subsequently reduce tissue-polymer contact, by over 75%. This stent design was previously used on the durable polymer, paclitaxel-eluting CoStar stent (Conor MedSystems, Palo Alto, CA). Unfortunately, despite promising initial results,[147–149] the CoStar stent failed to develop following disappointing results from the CoStar II study,[150] where it was shown not to be noninferior to the TAXUS PES with respect to clinical outcomes in terms of MACE (CoStar 11.0% vs. PES 6.9%, $p = 0.005$), and angiographic outcomes such as in-stent late loss (CoStar 0.49 mm vs. PES 0.18 mm, $p < 0.0001$). The failure of the stent was attributed to several factors including changes in the manufacturing process during the trial that may have affected the paclitaxel release kinetics and the small number of patients in the earlier studies. Perhaps of greatest relevance was that the dose of paclitaxel, which was reduced in an attempt to maximize long-term safety, may have been too low to inhibit neointimal hyperplasia. Learning from this, the NEVO stent has the same sirolimus dose and release kinetics as found on the Cypher SES, thus ensuring that drug elution is complete within 90 days.

The stent has so far only been evaluated in the NEVO-RES I study, which was a randomized, multicenter, noninferiority study comparing the NEVO™ stent to the TAXUS™ Liberté PES stent in 394 patients with single *de novo* coronary artery lesions. At 6-month angiographic follow-up, the primary endpoint of in-stent late lumen loss was significantly lower in patients treated with the NEVO stent (0.13 vs. 0.36 mm, $p < 0.0001$); a superiority which was preserved irrespective of diabetic status, lesion length, or vessel diameter.[151] Clinical endpoints at both 6 and 12 months were numerically lower in the NEVO treated group, although these differences did not reach significance. The rate of ST was 0.0% and 1.1% ($p = 0.24$) in patients treated with the NEVO and PES stent, respectively.

A more extensive evaluation of the NEVO stent is in the currently enrolling NEVO-II study, which will randomize 2500 'all-comers' in a 2:1 ratio to treatment with either the NEVO™ stent (1667) or the Xience V EES (883) stent, with a primary endpoint of target vessel failure at 12 months, and angiographic follow-up in a subset of patients planned at 13 months. Similarly, the NEVO-III will enroll 1300 US patients in a nonrandomized registry.

6.627.8.1.3. Paclitaxel-eluting DES with biodegradable polymers

- JACTAX™ stent (Boston Scientific, Natick, MA, USA)

The JACTAX™ Liberté PES stent is a stainless steel PES stent, which utilizes a novel abluminal PLA biodegradable polymer, known as the Juxtaposed Abluminal Coating technology (JAC™). This polymer, which is fully resorbed within 6–9 months and controls the release of paclitaxel over 90 days,

has a microdrop structure such that the 16 mm JACTAX™ stent has 2700 microdots, each containing 3.4 ng of polymer (total 9.2 μg, Figure 13). The thickness of the polymer (≤1 μm) is ~18 times less than that found on the TAXUS Liberté stent, while the corresponding polymer mass is 100 times less.

The JACTAX™ stent is currently being evaluated with a coating of either low (LD) or high dose (HD) paclitaxel. The JACTAX HD FIM study[152] has recently reported 9-month clinical and angiographic results among a cohort of 103 patients treated with the JACTAX HD stent, who were compared to 217 historical matched controls treated with the TAXUS Liberté stent from the ATLAS study.[70] The primary endpoint of MACE achieved the prespecified criterion for noninferiority; moreover there were no deaths, Q-wave MIs, or ST during follow-up. Finally, there were also no significant differences in the angiographic endpoints of in-stent late loss (0.33 vs. 0.39 mm, $p = 0.36$) and binary restenosis (5.2% vs. 9.2%, $p = 0.22$).

Clinical evaluation of the JACTAX™ LD stent is currently on-going in the JACTAX LD DES Trial, which is randomizing 130 patients to treatment with either the JACTAX™ LD stent or the TAXUS Liberté stent; the primary endpoint is MACE at 9-month follow-up. Additional studies are planned to evaluate this new polymer technology on different stent platforms including a platinum–chromium alloy (Element™ stent platform, Boston Scientific, Natick, USA) and in combination with everolimus on the JacPro™ stent (Boston Scientific, Natick, USA).[153]

6.627.8.2. Polymer-Free DES

Nonpolymeric stents offer the potential advantages of avoiding the long-term adverse effects of a polymer, improved healing, and an improvement in the integrity of the stent's surface because no polymer is present that can be peeled off the struts. Several different techniques are available to enable drug elution from stents in the absence of a polymer:

(1) The bioactive substance can be directly attached to the stent surface using covalent bonding, or crystallization–chemical precipitation on the stent surface.
(2) The bioactive agent can be dissolved in a nonpolymeric biodegradable carrier on the stent surface.
(3) The bioactive agent in its pure form can be impregnated into the porous surface of the stent, or the stent's body.

A brief over view of the available polymer-free stents is given below.

6.627.8.2.1. BioFreedom biolimus A9-eluting stent

This BioFreedom (Biosensors, Morges, Switerzland) 316L stainless steel stent elutes biolimus A9 without the presence of a polymer. Preclinical studies in the porcine model have reported lower injury scores; fewer struts with fibrin, granulomas, and giant cells; significantly lower percentage diameter stenosis; and greater endothelialization with the BioFreedom stent when compared to SES at 180-day follow-up.[154]

The only clinical trial performed so far enrolled 75 low-risk patients with *de novo* lesions, who were randomized to treatment with either a standard dose BioFreedom stent (15.6 μg mm^{-1}), a low dose BioFreedom stent (7.8 μg mm^{-1}), or a TAXUS PES. At 4-month angiographic follow-up, the in-stent late loss was 0.08, 0.12, and 0.37 mm for the standard dose BioFreedom stent, low dose BioFreedom stent, and TAXUS PES, respectively (Standard dose vs. TAXUS $p < 0.001$; low dose vs. TAXUS $p = 0.002$). At 4-month follow-up, there were no MACE or ST events with either the standard dose BioFreedom stent or the TAXUS PES. Clinical evaluation in larger patient populations is on-going.[155]

6.627.8.2.2. VESTAsyn sirolimus-eluting stent

The VESTAsyn SES (MIV Therapeutics, Atlanta, GA) is a polymer-free stainless stent which has a nanothin, microporous, hydroxyapatite surface coating impregnated with 55-μg dose of sirolimus (Figure 14(a) and 14(b)). Sirolimus is eluted over 90 days, while the hydroxyapatite remains stable over the first 4 months, before completely dissolving around 9–12 months after stent implantation. Preclinical studies indicate that the low dose of sirolimus, which is made possible by the hydroxyapatite platform, results in reduced signs of delayed vascular healing, suggesting less local toxicity, and a faster healing response.[156]

Primary evaluation of the stent took place in the 15 patients of the VESTAsync I FIM study.[157] At 4- and 9-month angiographic follow-up, effective reductions in late loss and intimal hyperplasia were observed, with no evidence of 'late-catch' seen on quantitative coronary angiography (QCA) or IVUS. Up to 3-year follow-up, the only clinic event was a single TLR.[158] Needless to say, randomized trials in more complex patient populations are planned, including the VESTAsyncII study which will enroll 75 patients randomized 3:1 to either

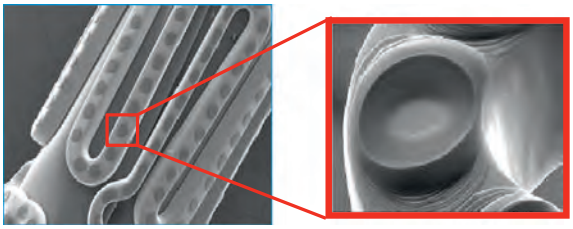

Figure 13 Scanning electron microscopy of the JACTAX paclitaxel-eluting stent. The image and insert demonstrate the microdrop structure of the Juxtaposed Abluminal Coating in use on the stent. Courtesy of Boston Scientific, Natick, USA.

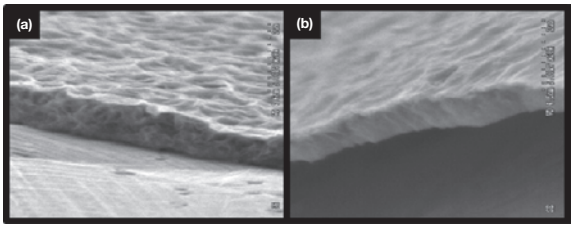

Figure 14 The polymer-free VESTAsyn stents have a (a) rough surface because of their hydroxyapatite coating; however this is (b) smoothed over following the addition of 0.6-μm coating of sirolimus.

the VESTAsyn SES or a control BMS, with a primary endpoint of late loss at 8-month follow-up.[158]

6.627.8.2.3. YUKON: sirolimus-eluting stent

The stainless steel YUKON SES (Translumina, Germany) was the first and consequently now the most extensively studied polymer-free DES. The stent has a microporous surface, with pores that are 2-μm deep and effectively function as a drug reservoir removing the need for a polymer.[159] Uniquely, the dose of sirolimus is customized in the cath lab, just prior to stent implantation, in a coating process taking ~8 min. Initial studies have established that the optimal concentration of rapamycin to prevent restenosis and TLR is 2%.[160]

After complete drug release, the remaining microporous surface appears to favor the adhesion of endothelial cells, a hypothesis initially suggested by angiographic follow-up data,[161] and now confirmed by OCT, which has demonstrated significantly greater neointimal thickening and stent strut coverage with the YUKON stent compared to SES at 3-month follow-up.[162] Clinical studies including both registry and randomized data demonstrate noninferiority of a YUKON stent eluting 2% rapamycin when compared with PES out to 1-year follow-up.[163,164]

Observation data extending out to 2-year follow-up have indicated that the YUKON stent is less susceptible to delayed restenosis than the conventional DES. Of note, Byrne *et al.* reported a significantly lower change in late loss between 6 and 8 months and 2 years for the YUKON stent, when compared with SES and PES (YUKON 0.01 ± 0.42 mm, SES 0.17 ± 0.50 mm, and PES 0.13 ± 0.50 mm, $p < 0.001$).[165] This important finding has also been observed during similar 2-year follow-up of the ISAR-TEST 2 and ISAR-TEST-3 studies, both of which randomized patients to treatment with polymer-free stents, or either conventional polymer or biodegradable polymer DES.[166–169] Collectively these results suggest that polymer-free stents may not be subject to the 'late-catch' phenomenon which has been reported with permanent polymer DES, and appears to be worse in those stents eluting macrocylic lactone derived antiproliferative coatings.[121,170,171]

6.627.8.3. DES Made from New Metal Alloys

Two new DESs, the PROMUS Element and the TAXUS Element (Boston Scientific, Natick, MA), both utilizing a platinum–chromium alloy have recently gained C.E mark approval. This new stent alloy, whose composition is compared to other stent platforms in **Table 3**, offers several distinct advantages over conventional stent materials. Platinum is two times more dense than iron or cobalt, malleable, corrosion resistant, and fully incorporated into the platinum–chromium alloy. Consequently the platinum–chromium stent offers the advantages of increased radio-opacity and thinner stent struts, which as previously discussed confer distinct advantages in terms of potential reductions in restenosis and improved clinical outcomes (**Figure 8**);[70–72,96,97] however, these must be balanced with the potential reduction in radial force and increase in acute recoil. However, encouraging initial bench mark studies have indicated that despite thinner struts, the platinum–chromium alloy stent has better radial strength, lower acute recoil, and better vessel conformability compared to conventional stent platforms; **Table 4**. In addition, rates of uncovered stent struts have been shown to be lower with the Element stent when compared with the stainless steel Liberté and Express stents at 14 days.

6.627.8.3.1. TAXUS element

The TAXUS Element stent (**Figure 15**) has a poly(styrene-*b*-isobutylene-*b*-styrene) polymer, which facilitates controlled elution of paclitaxel (concentration 1 $\mu g\,mm^{-2}$) in an identical pattern to that seen on the stainless steel TAXUS Liberté and Express stent. The TAXUS Element is currently being assessed in the PERSEUS (A Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the use of the TAXUS Element Paclitaxel Eluting Coronary Stent System for the Treatment of De Novo Coronary Artery Lesions) clinical trial program, which includes the following features:[172,173]

- The PERSEUS Workhorse trial randomized 1262 patients, with lesions <28-mm long, in vessels between 2.75–4.00 mm in diameter, to treatment with the TAXUS Element ($n = 942$) or the TAXUS Express PES ($n = 320$).[172] At 12-month clinical follow-up, the rate of TVF, the primary endpoint, was Element 5.6% and Express 6.1%, which met the prespecified criterion for noninferiority. The secondary endpoint, percent diameter stenosis at 9-month angiographic follow-up also met the prespecified criterion for noninferiority. In addition, no significant differences were seen between stents with respect to late loss (Element 0.34 ± 0.55 mm vs. Express 0.26 ± 0.52 mm, $p = 0.33$), or other the clinical points such as MACE, mortality, MI, and ST.
- The PERSEUS Small vessel trial compared the TAXUS Element stent to historical BMS controls in patients with

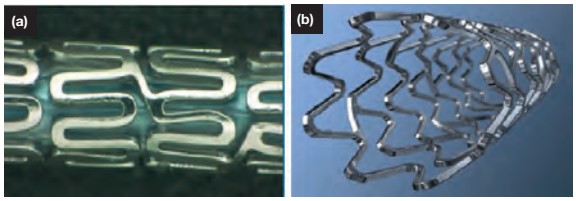

Figure 15 The platinum–chromium Element stent crimped (a) and expanded (b). Courtesy of Boston Scientific, Natick, USA.

lesions which were <20 mm long, in vessels between 2.25–2.75 mm in diameter.[173] Overall, the study enrolled 224 patients treated with the Element stent, who were compared to 125 lesion-matched historical controls treated with a BMS from the TAXUS IV study. Results at 9-month follow-up demonstrated a significantly lower in-stent late loss (the primary endpoint) with the Element stent compared to the BMS stent (0.38 ± 0.51 vs. 0.80 ± 0.53 mm, $p < 0.001$). At 12-month follow-up, the rates of target lesion failure and MACE were both significantly lower with the Element stent, while safety endpoints and ST were comparable between both stents.

6.627.8.3.2. PROMUS element

The PROMUS Element stent has a PBMA primer coating, a PVDF-HFP polymer, and is loaded with 1 μg mm^{-2} of everolimus, 87% of which is eluted within 90 days of stent implantation. No clinical data are available at present; however, the stent is undergoing evaluation in the PLATINUM clinical trial program comprising the following studies:[153]

- The fully enrolled multicenter PLATINUM Workhorse noninferiority study which randomized 1532 patients to treatment with the PROMUS Element or PROMUS Xience V EES stent (Boston Scientific, Natick, M). Results are expected in late 2010.
- The single-arm PLATINUM Small vessel study which will enrol 94 patients with lesions in vessels between 2.25 and 2.5 mm.
- The single-arm PLATINUM Long lesion study which will enrol 102 patients with lesions between 24 and 34 mm in length.
- The single-arm PLATINUM QCA study which will assess QCA in 100 patients at 9-month follow-up.

6.627.8.4. Nitinol Stents

In recent times, there has been increasing interest in the use of nitinol as a platform for coronary stents. Nitinol, which is an alloy of nickel and titanium, has shape memory property, which has resulted in its use in self-expanded coronary stents that have been specifically designed for dedicated coronary lesions such as those in small vessels, those at bifurcations, and those due to vulnerable plaque. In addition, the alloy also has other notable properties which make it favorable for use as a coronary stent platform, namely it is biocompatible, fatigue resistant, and has superelastic properties, which allow it to withstand large amounts of recoverable strain.

Historically, the early stents to be implanted in coronary arteries were self-expanding stents;[7] however, they were eventually replaced by balloon-expandable stents which are currently the preferred type of stents. Of note, self-expanding stents offer important advantages over conventional balloon-expandable stents which include a lower incidence of edge dissections; reduced rates of side-branch occlusion and no-reflow; positive remodeling; and reduced immediate vessel wall injury which may lead to a reduction in neointimal hyperplasia and a larger vessel lumen.[174–176]

Despite these potential advantages, there are some drawbacks of self-expanding stents which are related to their delivery systems and properties:

- *Delivery systems*: Self-expanding stents are housed within a delivery catheter that ensures stent security; however, these catheters can be cumbersome to use, and have an associated learning curve. The delivery profile of these stents is dictated by strut dimensions, as opposed to the balloon profile as in balloon-expandable stents.
- *Mechanical properties*: The continued outward radial force that self-expanding stents exert even after deployment leads to negative chronic recoil, and results in a larger vessel at follow-up. This phenomenon can make matching stent size to vessel size difficult. Secondly, self-expanding stents foreshorten on expansion and/or can move forward because of spring movements when the stent is released from the delivery system; these properties can make accurate placement difficult.

Recently reductions in strut thickness, improvements in delivery systems, and the addition of a drug coating have lead to increased interest in self-expanding stents for the treatment of the following types of lesion.

6.627.8.4.1. Lesions in small vessels

The use of balloon-expandable stents to treat lesions in small diameter coronary arteries is associated with a risk of edge dissection, owing to the high pressures required for optimal stents implantation. Ample evidence exists relating inadequate stent strut apposition, and stent expansion to a subsequent increased risk of restenosis and ST.[134] As stated previously, self-expandable stents offer the advantage of minimizing baro-trauma and the risk of edge dissections, and therefore have a potential role in the treatment of small vessel lesions.

The Cardiomind Sparrow™ (Cardiomind Inc, Sunnyvale, CA) is a small profile nitinol self-expanding stent that is designed specifically for treating lesions in coronary vessels with a diameter of between 2.00 and 2.75 mm (**Figure 16(a)**).

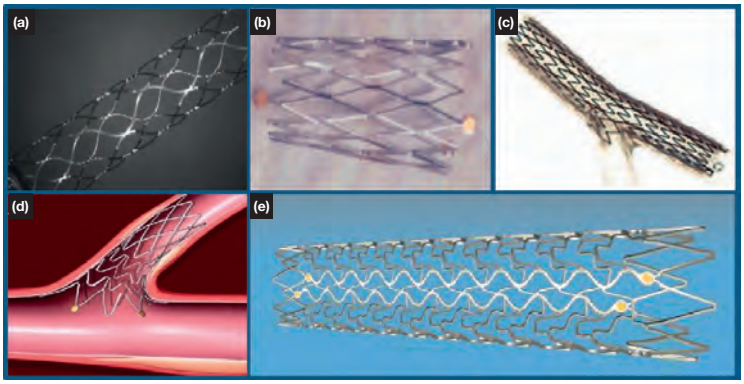

Figure 16 Self-expanding nitinol stents (a) The CardioMind Sparrow stent, (b) Axxess bifurcation stent, (c) Stentys bifurcation stent, (d) Capella side-branch stent, and (e) the vProtect® Luminal Shield stent.

The stent, which has a strut thickness of 61 μm, is preloaded on a 0.014″ guidewire, with 2–3 cm of radio-opaque guidewire at the distal end enabling positioning within the vessel. A dedicated delivery system is used to deploy the stent. The uncoated stent has been assessed in the CARE I feasibility study, which recruited 21 patients with *de novo* lesions in vessels 2.0–2.5 mm in diameter. A 13% rise in the in-stent volume index was observed at 6 months, together with a binary restenosis rate of 20%. There was no ST at 30 days, and two MACE events occurred through to 24-month follow-up. These patients have subsequently been compared to a group of historical controls, treated under the same inclusion and exclusion criteria, but with implantation of a balloon-expandable stent. Results demonstrate a significantly lower in-stent late lumen loss (0.73 vs. 1.11 mm, $p = 0.04$), and intimal hyperplasia volume obstruction (31.9% vs. 39.9%, $p < 0.001$) with the Cardiomind stent.[177,178]

The next-generation Sparrow stent has a strut thickness of 67 μm and is coated with a 4-μm thick layer of sirolimus at a dose of 6 μg mm^{-1}, and an 8-μm thick layer of biodegradable PLA/PGLA polymer. It is currently being assessed in the CARE-II study that will randomize 220 patients with lesions ≤20 mm in length, in vessels between 2.00 and 2.75 mm in diameter to treatment with the bare-metal Cardiomind Sparrow™, the drug coated Cardiomind Sparrow™, or a BMS. Interim results at 8-month follow-up are expected in 2010.[179]

6.627.8.4.2. Lesions in bifurcation

Bifurcation lesions remain a challenging lesion subset for today's interventional cardiologist. Discussion continues over the optimal number of stents to implant and the stenting technique to use; however, the wide anatomical variation in bifurcation lesions suggests that no optimal strategy suitable for all will be established. In view of these ongoing issues, some dedicated bifurcation stents have been developed, some of which utilize nitinol in view of its ability to conform more optimally to angulated coronary anatomy, compared to conventional balloon-expandable stents.[180,181]

The following are three such stents:

- Axxess™ (Devax, Irvine, CA)

This conical nitinol stent has a strut thickness of 152 μm, and is coated with a biodegradable PLA polymer, which degrades over 6–9 months, and release the macrocylic lactone biolimus A9 (**Figure 16(b)**). The stent is released by withdrawing a covering sheath, and is ideally placed at the level of bifurcation carina, allowing easy access to both distal branches, which can be stented if required. The stent has been assessed in the DIVERGE (Drug-Eluting Stent Intervention for Treating Side Branches Effectively) registry which recruited 302 patients who were followed-up for 9 months. Of note, additional stent implantation was required in 64.7% of patients. At 9-month angiographic follow-up, in-stent late loss was 0.29 mm in both branches, while the rates of binary in-stent restenosis were 2.3% and 4.8% in the main-branch and side-branch, respectively. Clinical event rates at follow-up were low with a rate of MACE of 7.7%, TLR 6.4%, and ST 1%.[182]

- StenTys™ (Stentys, SAS, France)

This paclitaxel-eluting self-expanding stent is made of a z-shaped mesh linked by small interconnections (**Figure 16 (c)**). It consists of a preformed main-branch stent with side ports to facilitate access to the side-branch. Uniquely, the stent struts can be disconnected with the use of an angioplasty balloon; therefore, an opening for the side-branch can be created anywhere in the stent after it is implanted; the disconnected struts can subsequently scaffold the ostium of the side-branch. Evaluation of the stent has been performed in the OPEN (Stentys coronary bifurcation stent system for the percutaneous treatment of *de novo* lesions in native bifurcated coronary arteries) study which enrolled 40 patients and reported a low rate of additional stent implantation (main-branch 9%, side-branch 13%). Angiographic follow-up at 6 months demonstrated a late loss of 0.83 mm and a binary in-stent restenosis rate of 25% and 14% in the main- and side-branch, respectively. The rates of MACE, death, MI, and TLR were 5.1%, 0.0%, 2.5%, and 2.5%, respectively.[183,184]

- Cappella Sideguard™ (Cappella Inc, Auburndale, MA)

This nitinol stent is shaped like a trumpet (**Figure 16(d)**), to allow excellent conformability to vessel anatomy and is designed for bifurcation lesions with significant side-branch disease. It is implanted in the ostium of the side-branch, and facilitates conventional stent implantation in the main-branch without restriction. The stent has been evaluated in the 93 patient Sideguard I and II FIM studies. Encouraging at 12-month follow-up, angiographic in-stent late loss in this bare-metal stent was 0.21 and 0.58 mm in the main- and side-branch, respectively. With respect to clinical outcomes, the rates of cardiac death were 1.2%, MI 3.6%, and TLR 7.2%.[185,186]

6.627.8.4.3. Lesions due to vulnerable plaque

Data indicate that unstable presentations such as MIs are commonly the result of a disruption of thin-cap fibroatheromas (TCFAs).[187] It follows that preemptive treatment of these lesions involves preventing cap rupture, and promoting endothelialization. The very nature of these thin-cap lesions indicates that the high deployment pressures required for implantation of a balloon-expandable stent are undesired. Advantageously, self-expanding stents do not induce vessel injury during implantation, thereby minimizing the risk of embolizing necrotic material and thrombus distally. In the long-term, the lack of strut penetration into necrotic core may reduce the risk of ST, which may occur through the substantially delayed arterial healing that occurs when struts penetrate necrotic core.[188,189] The vProtect® Luminal Shield (Prescient Medical, Inc., Doylestown, PA) is a self-expanding nitinol stent (**Figure 16(e)**) which has been shown in animal studies to promote vascular healing, and importantly, achieve complete endothelialization of the stented segment within 7 days.[190] Encouragingly, data from the FIM study has demonstrated that the 'shield' can induce plaque remodeling, and has a positive vascular healing profile as demonstrated on IVUS. The randomized SECRITT I (Santorini Criteria for Investigating and Treating Thin Capped Fibroatheroma Trial) is currently evaluating the safety and feasibility of stenting a vulnerable plaque with the vProtect® Luminal Shield compared with a medically treated, nonstented (control) group.[191]

6.627.9. Less Successful Medications on DES

Apart from the drugs that have made it on to mainstream workhorse DES in catheterization labs around the world and those which are currently being tested, many have been tried with less than satisfactory results. The following are three such examples:

- Tacrolimus

Tacroliumus (FK506) (**Figure 5**) is a water-insoluble macrolide immunosuppressant produced by *Streptomyces tsukubaensism*, whose drug formulation (Prograf) is commonly used to prevent allograft rejection after organ transplantation. Its inhibitory effect, which is greatest on smooth muscle cells rather than endothelial cells, is mediated by means of its cytostatic effect, holding cells in their G_0 or resting phase.

In the Janus tacrolimus-eluting stent (Sorin Biomedica Cardio, Saluggia, Italy), the drug is embedded in reservoirs on the outer stent surface that allow release of the drug toward the vessel wall only. The stent also has an integrated thromboresistant carbofilm coating the whole stent surface. The largest assessment of the stent took place in the JUPITER-II trial, which randomized 332 patients to treatment with either the Janus tacrolimus-eluting stent or a carbofilm coated BMS. Despite a low frequency of clinical outcomes, which were nevertheless comparable between groups, angiographic results were disappointing, with no significant differences seen in the mean in-stent late lumen loss (tacrolimus-eluting stent 0.65 ± 0.47 vs. BMS 0.66 ± 0.53 mm).[192]

Further studies of DES-eluting tacrolimus include the evaluation of the MAHOROBA stent (Kaneka, Osaka, Japan), which had a cobalt–chromium stent platform and eluted tacrolimus from a bioabsorbable polymer (poly-DL-lactide-coglycolide). In the 47 patient FIM study, a 4-month in-stent late loss of 0.99 ± 0.46 mm and an IVUS determined in-stent % volume obstruction of $34.8 \pm 15.8\%$ reconfirmed the absence of any clinical advantage with use of this drug.[88,89]

- Pimecrolimus

Although pimecrolimus (**Figure 5**) is part of the 'Limus' family, it does not block mTOR, and therefore it has limited effects that are mediated through an anti-inflammatory action on endothelial proliferation. The FIM study with 15 patients showed a high rate of angiographic restenosis (61%), mean late loss (1.44 mm), and TLR (53%) at 6 months.[193] Further assessment of this drug took place in the ProLimus trial, which evaluated a cobalt–chromium pimecrolimus-eluting stent with a biodegradable polymer. The study enrolled 61 patients with relatively simple coronary lesions and had a MACE rate of 18% at 6 months, which actually achieved the study's primary endpoint of a 6-month MACE rate below 20%. Nevertheless, the late loss was 1.11 ± 0.65 mm, the rate of binary restenosis was 32.7% and the rate of TLR was 32.8%, thereby demonstrating an overall inferior antirestenotic effect of the pimecrolimus stent, compared to results from other established DESs.[194]

Pimecrolimus has also been combined with other antiproliferative agents with the hope that a synergistic effect would ultimately improve its overall neointimal inhibitory effect. The GENESIS trial randomized 246 patients to treatment with the PES CoStar stent ($n = 49$, Conor Medsystems, Menlo Park, CA); the SymBio stent, which eluted a combination of pimecrolimus and paclitaxel ($n = 97$); and the pimecrolimus-eluting Corio stent ($n = 100$).[195] The trial was prematurely suspended with the in-stent late lumen loss being significantly lower with the CoStar compared to either the SymBio or Corio stent (PES 0.58 ± 0.58 mm vs. PES/pimecrolimus 0.96 ± 0.73 mm and PES 0.58 ± 0.58 mm vs. pimecrolimus 1.40 ± 0.67 mm, $p < 0.001$ for both comparisons).

These results were consistent with other studies of the pimecrolimus-eluting stent, and thus are more reflective of the lack of efficacy of pimecrolimus rather than a lack of benefit in the use of dual DESs. Of note, the benefit of dual drug elution has been suggested by results of the ISAR-TEST 3 study, which demonstrated comparable clinical outcomes and a durable antirestenotic efficacy out to 2 years with a polymer-free stent eluting a combination of sirolimus and the antioxidant probucol, when compared to SES and E-ZES.[166,168]

- Estradiols

Experimental studies have suggested that estradiols can improve vascular healing, reduce smooth muscle cell migration and proliferation, and promote local angiogenesis.[196–198] In addition, animal data have indicated that local delivery of estradiol can inhibit neointimal hyperplasia, and also promote endothelial repair and recovery.[199–202]

The feasibility of using 17-β-estradiol to inhibit restenosis in humans was first assessed in the EASTER study, which enrolled 30 patients who received a 17-β-estradiol BiodivYsio (Biocompatibles Ltd., London, UK) stent in a *de novo* coronary lesion. Similar to the preclinical data, results were encouraging with a 6-month in-stent and in-segment late loss of 0.57 and 0.32 mm, respectively, and only one repeat revascularization.[203]

These promising results were further assessed in the ETHOS I study, which randomized 95 patients to treatment with a BMS ($n = 32$), a moderate-release estradiol-eluting stent ($n = 31$), or a slow-release estradiol-eluting stent ($n = 32$).[204] Despite good tolerability of the stent, the study disappointingly demonstrated no advantage from the use of the oestradiol stent over the BMS at 6-month follow-up. In particular, there were no significant differences between the three groups in the intravascular endpoints of neointimal hyperplasia volume, volumetric plaque burden, and in-stent volume obstruction; the angiographic endpoints of in-stent binary restenosis and in-stent late loss; and the clinical endpoints of TLR and MACE.

This lack of benefit from using a 17-β-estradiol-coated stent has been subsequently confirmed in two additional randomized trials.[205,206] Airoldi *et al.* randomized 108 patients to treatment with an estrodiol-eluting stent ($n = 54$) or a phosphorylcholine-coated stent ($n = 54$) and observed no between stent differences with respect to angiographic or clinical outcomes at 1-year follow-up.[206] In the ISAR-PEACE study, which is the largest evaluation of 17-β-estradiol-eluting stents, 508 patients with *de novo* lesions were randomized to treatment with a polymer-free estradiol plus rapamycin stent or a polymer-free rapamycin stent alone.[205] Angiographic follow-up at 6–8 months and clinical follow-up at 12 months failed to demonstrate any advantage with the addition of estradiol to a rapamycin-eluting stent.

6.627.10. Conclusions

Coronary stents have undisputedly revolutionized the treatment of patients with CAD; however, an element of concern remains regarding their long-term safety. In an effort to address some of these concerns, second generation DESs were developed and they have already demonstrated an overall improvement in the outcomes seen with the first generation DESs. Currently, a vast number of new stent designs are being evaluated and only time will tell if these newer stents will lead to further meaningful improvements in clinical outcomes and safety. A step further from stent implantation is the concept of restoring normal vascular function through the use of devices which completely biodegrade. This exciting new concept of completely biodegradable implants is explored in the next chapter.

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1.2 Transferability of data between different drug-eluting stents.

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Transferability of data between different drug-eluting stents

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The introduction of drug-eluting stents (DES) for the treatment of coronary artery disease has considerably influenced the market size and growth rates for coronary stents. Companies are continuously striving to develop stents that are the safest and most effective with the goal of being market leaders. Since a considerable number of stents have been developed to date, and head-to-head comparisons in medical literature indicate the ones with the best results, it is no surprise that last generation DES systems tend to be an iterative progression from the previous successful generation. As a result, regulatory bodies including the Food and Drug Administration (FDA) and Conformité Européene (CE), who are consulted by the companies during a new DES development, have to decide whether the changes made to the stent system are significant or not. This in turn will directly influence the amount of additional non-clinical and/or clinical testing that is needed to support the safety and efficacy of the modified DES. Differences in decisions taken between the regulatory bodies is not unknown in this situation, and stems from our lack of understanding concerning what constitutes significant and non-significant change.

Guidelines from the FDA[1] and CE[2] refer to changes or modifications in the various components of the stent system to come to a conclusion as to whether the new stent is novel (innovative) or simply equivalent with minor modifications from the previous device. In principle, novel DES with unique characteristics dissimilar to any currently approved coronary stent should be tested extensively, since its ultimate effect on clinical outcome is unknown and unpredictable. On the other hand, slight modification in one component or in the manufacturing methods of a stent system needs limited investigation prior to approval, since such changes are not expected to affect the clinical outcome in a negative way. Thus, a spectrum of intensity of required investigations exists; these range from: pharmacokinetic tests, benchmark tests, animal studies, first-in-human and fully randomised clinical trials for novel stent systems, registries, or even just transferability of data (from literature) from old stent to the new stent system in the case of minor modifications. Therefore, the classification of the new stent system has a tremendous impact on the amount of investigations – and therefore the time and money required – which in turn affect the competitiveness of the stent once it makes it to the production line of the company.

To understand the significance of a change in a DES system we need to evaluate the importance of that particular component in the performance of the stent. Probably the best form of analysis of such a change would be a randomised controlled trial (RCT) sufficiently powered for demonstration of superiority or non-inferiority – of at least one year and preferably with five-year follow-up – comparing two stents which differ only in the component under investigation in terms of clinical endpoints as defined by the Academic Research Consortium.[3] In essence, target vessel revascularisation (TVR) is a measure of effectiveness of the device while myocardial infarction and cardiac mortality is a measure of its safety. Short of that, imaging endpoints that have been validated as surrogate markers of clinical outcome can be utilised. However, such endpoints are only accepted for "certain second generation DES…in specific populations or in specific vessel or lesion types"[1]. Although histopathological animal studies are an important part of the work-up in an innovative stent system, the short-term results do not provide sufficient information to judge the safety and efficacy of a DES as demonstrated in the ACTION trial[4].

Drug type

The type of drug used, is the most well known component which affects clinical outcomes. In the recent SPIRIT trials, everolimus eluting stents were shown to be superior to paclitaxel eluting stents[5]. Although the major difference between the two-stent systems is the drug, the likely explanation of fewer periprocedural myocardial infarctions may be due to other stent characteristics, including smaller strut size (81 µm vs 132 µm), thinner polymer thickness (7.8 µm vs 16 µm) and less polymer webbing which could have resulted in less side branch compromise.

Polymer and drug release profile

The drug release profile which depends on the drug dose, chemical composition and drug/polymer composition as well as the way it is applied to the stent platform also influences stent performance. The release kinetics of the drug are also proportional to the surface area, and inversely proportional to the membrane thickness. Thus, application of a studied drug/polymer to a stent with different design and/or different strut thickness and surface area may change the performance of the new DES. In PISCES, variable dose and release kinetics were shown to affect neointimal hyperplasia as demonstrated with the lowest in-stent late loss observed with the 10 µg and 30 µg doses in 30-day release groups respectively.[6]

Most of the other stent systems use a polymer that coats the stent surface and a polymer/drug combination in specific weight-to-weight ratio which determines the release profile of the drug. The impact of a novel durable polymer matrix (Biolinx™) which prolongs zotarolimus elution (despite same dose) in the Endeavor Resolute DES system was assessed in the Resolute trial[7].

Fourth-generation DES currently under development employ an ultra-thin biodegradable abluminal polymer that delivers a very low dose of paclitaxel to the wall of the treated vessel, and no polymer or drug on the inner surface of the stent. Being a major, significant change, the stent is undergoing complete evaluation, including pivotal trials.

Material composition of stent platforms

The alloy or modifications made to the composition of the stent platform is known to affect stent performance as exemplified in the NUGGET study, which showed worse angiographic and IVUS parameters at six months in the gold-coated NIR when compared to same uncoated stainless steel stent.[8]

A new platinum chromium alloy in the Promus Element, which uses the same drug and polymer as in Xience V (or PROMUS), was considered significant by the FDA and is thus being investigated in the PLATINUM trial, a single, blind, safety/efficacy randomised trial with parallel assignment to the PROMUS (cobalt chromium) and PROMUS Element. Is this truly a novel change, or is it iterative? Will CE mark be awarded, or will the decision be the same as the FDA's? Will the $10 million being spent for an RCT be money down the drain, or will it enlighten us to better understand the significance of alloy change?

Differences in strut thickness and stent design

Also in the bare metal stent (BMS) era, a randomised, multicentre trial showed significant differences in one year event free survival, freedom from myocardial infarctions and diameter stenosis at six months of 1,147 patients who received one of five stainless steel stents with different stent designs (Inflow, Multi-Link, NIR, Palmaz-Schatz and PURA-A)[9]. The degree of scaffolding, recoil, flexibility and deliverability of the stent are dependent on the stent design, and can influence procedural success rates as well as long term performance of the stent. Surface properties of particular stent designs can also be different, and may influence the stent interaction within the vascular wall in terms of vascular injury and inflammatory response. In DES the mechanism is modified by the anti-proliferative action of the drug but we can still hypothesize that the stent design influences procedural success.

The effect of strut thickness and the combination with stent design were studied in the ISAR-STEREO studies. Two stents with comparable BMS designs, but with stent thickness of 50 µm and 140 µm, were compared[10]. The incidence of angiographic restenosis and TVR were less in the thin strut group. In a second study, two different stent designs, a multi-link stent and a BX Velocity stent with different strut thickness (50 µm vs 140 µm), were compared. The incidence of angiographic restenosis was again lower in the thin strut group, as was TVR[11]. In both studies, no significant differences was observed in the combined incidence of death and MI at one year between the groups. These studies suggest that stent thickness may be a more important contributor than design for efficacy, at least in BMS. In DES, the newer continuous cell design and thin struts (0.0038") in Taxus Liberté were shown to be non-inferior to historic controls using the multi-link design with thicker (0.0052") struts in Taxus Express in the ATLAS trial[12]. Although the Liberté group had significantly more complex lesions, there was improved procedural performance with the newer stent as measured by lower procedure time, decreased bail-out and geographic miss as measured by quantitative coronary angiography. Here again, the combination of both strut thickness and stent design has influenced these results.

Changes in the design of the multi-link system and in the stent delivery system in Xience PRIME (Abbott Vascular) aimed at improving deliverability and flexibility of the everolimus eluting stent (Xience V) were considered iterative by the CE, while the FDA requested a registry pre-marketing. Improvement in the delivery system theoretically enhances procedural performance of the stents. The regulatory bodies limit the requirements to testing the delivery system using the intended DES/delivery system combination.

Differences in quality of manufacture of a stent can theoretically effect stent performance *in vivo* – a plausible explanation for the poorer outcome for the CoStar stent in the COSTAR II trial when compared to the same stent's previous safety and efficacy[13]. Critical process parameters should be controlled or monitored to ensure batch reproducibility and to minimise batch variability. If for example a stent is manufactured at one site by one company, can we assume that the end product is the same? Do minor differences in quality affect clinical results?

As such, the ultimate performance of a stent system depends on the contribution of each of the components and/or manufacturing standards individually – but also is affected by their combination – which could be either additive, synergistic, counteractive or the mixture of the three.

With the increasing number of companies investing in the development of newer stent systems, our regulatory bodies, scientific community and industry need to agree on which data can be transferable and which data has to be re-acquired. We need to stimulate collaboration of the interested parties to look into how the various components of the stent systems, and their combination, affect success or otherwise of a DES, to provide more robust scientific evidence for decisions taken by regulatory bodies which should then be unanimous. For this goal, a more uniform, homogenous and reproducible interpretation of registries and randomized controlled trials would be desirable.[14]

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Part II

PERCUTANEOUS REVASCULARIZATION IN STABLE CORONARY ARTERY DISEASE

2.1

Revascularization Treatment of Stable Coronary Artery Disease.

Magro M, Garg S, Serruys PW.

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Expert Opinion

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Revascularization treatment of stable coronary artery disease

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Introduction: Coronary artery disease (CAD) is the leading cause of mortality in developed countries. Angina, myocardial infarction, heart failure and other clinical manifestations of coronary atherosclerosis lead to considerable patient morbidity and constitute an increasingly heavy burden on health systems worldwide.

Areas covered: This article reviews the recent major developments in the treatment of CAD, which can be achieved using medical therapy either in isolation or in combination with revascularization, performed via coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI). There is no dispute that optimal medical treatment is the cornerstone of CAD management; however, timely revascularization offers superior symptom control in patients with severe symptoms and may also offer a survival advantage in some patients with diffuse disease and diabetes. Importantly, the advances in PCI technology, especially with the introduction of drug-eluting stents has narrowed the gap between CABG and PCI for the treatment of CAD.

Expert opinion: The continuous developments in diagnosis and treatment of CAD call for contemporary trials with detailed analysis to provide evidence that will help in the choice of the best and most cost-effective treatment strategy.

Keywords: angina, coronary artery bypass surgery, ischemic heart disease, percutaneous coronary intervention

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1. Introduction

The treatment of coronary artery disease (CAD) aims to relieve symptoms and myocardial ischemia; prevent acute events that are triggered by plaque rupture with subsequent myocardial damage a consequence of the embolization of atherothrombotic material or outright closure of the epicardial vessel; prevent progression of CAD, thereby reducing the risk of long-term complications of an ischemic cardiomyopathy such as congestive cardiac failure; and possibly to modify the natural history of the disease.

The choice of treatment modality therefore should be based on its ability to reach these targets in the most effective, safest and convenient way, keeping in mind both the patient's perspective and financial implications.

This review presents an update from recent developments and trials that target issues on the management of stable CAD, in patients with *de novo* coronary lesions (i.e., lesions that have not been treated previously), and thereby aims to promote evidence-based clinical practice. We highlight areas of controversy and those that warrant additional clinical research.

Article highlights.

- Anatomical and functional assessment of coronary artery disease (CAD) is essential for the optimal treatment strategy.
- Revascularization has a higher prognostic benefit than optimal medical therapy in patients with extensive vessel disease and significant myocardial ischemia.
- Optimal medical therapy remains a cornerstone in management of CAD.
- Coronary arteries with significant flow-limiting lesions as measured by noninvasive tests or fractional flow reserve can be revascularized, while those without significant obstruction can be safely deferred.
- The SYNTAX score is a useful tool to quantify extent and importance of CAD. Patients with complex CAD who have scores of up to 32 have similar clinical outcomes (major adverse cardiovascular and cerebrovascular events) when treated with percutaneous coronary intervention (PCI) and coronoary artery bypass surgery (CABG). Those with higher scores have better outcomes with CABG.
- Drug eluting stents have narrowed the advantage of CABG by dramatically decreasing the revascularization rates compared with bare metal stent use.
- Left main-stem disease, bifurcation lesions and chronic total occlusions are among the lesion subsets that still present a challenge for revascularization with PCI, but early data look promising.
- Diabetes and CAD represent a unique clinical state that is associated with a worse prognosis. More data with drug-eluting stents versus CABG are needed to clarify the equivalence of these revascularization strategies.
- Quality-of-life and cost-effectiveness analyses are increasingly important for the three treatment strategies and may affect decision making in cases in which clinically the modalities are shown to be equivalent.

This box summarizes key points contained in the article.

2. Presentation and diagnosis of coronary artery disease

The clinical presentation and diagnostic work-up of patients with anginal symptoms is crucial for appropriate decision making with regard to establishing an optimal treatment strategy. Understanding the inherent risks posed by the underlying CAD, and the risk–benefit balance of undertaking one or more of the available management strategies, helps clinicians and patients formulate the right therapeutic plan.

Age, gender and the presence of underlying risk factors such as diabetes, hypertension, hypercholesterolemia, smoking, body mass index, immobility and a patient's personality are among the most important factors to consider even before any diagnostic work-up. Risk-factor management by lifestyle measures including diet and exercise as well as pharmacological treatment has been shown to control CAD progression, control symptoms and prevent acute adverse cardiovascular events. Severity of clinical symptoms off treatment and improvement on treatment also provide essential information. Additionally, confirmation of underlying CAD with a diagnostic test is both desirable and important as it can provide both objective and prognostic information. This may even lead to changes in treatment strategy, such as more aggressive pharmacotherapy or outright revascularization.

Combined anatomical and functional information is ideal when it comes to diagnostic tests for CAD (**Table 1**). However, in real life, many patients, including those referred for revascularization, do not have information on both.

2.1 Anatomical versus functional tests for CAD diagnosis

2.1.1 Patients with a functional noninvasive test as the initial diagnostic test

CAD is still most commonly diagnosed using the gold-standard investigation, invasive coronary angiography, which is usually done following a positive noninvasive functional test such as an exercise stress test, stress echocardiography or a myocardial perfusion scan. The diagnostic modality is of significance as clear signs of ischemia on any of these modalities decrease uncertainty regarding the functional significance of a coronary artery lesion (in the appropriate territory) subsequently seen on angiography.

Patients referred with an 'inconclusive noninvasive test' in which CAD is subsequently discovered may need an additional functional test. One such test that can be performed in the cardiac catheterization laboratory at the time of diagnostic angiography is fractional flow reserve (FFR). Importantly, this can provide the necessary information to decide whether a coronary lesion is functionally significant and thereby in need of treatment [1].

2.1.2 Patients with an anatomical test as the initial diagnostic test

Multi-slice computed tomographic (MSCT) angiography is increasingly being used as the initial diagnostic test in patients with symptoms suggestive of ischemic heart disease. Patients who have an MSCT angiography can subsequently be referred for invasive diagnostic angiography either for clarification of a nondiagnostic test with suboptimal image quality or for direct treatment of an apparently significant coronary lesion. These patients often have no other functional test, and an on-table FFR is warranted if the lesion is < 90% diameter stenosis [2]. A simple anatomical classification into one-, two- or three-vessel disease can provide adequate risk stratification, as has been demonstrated by the Coronary Artery Surgery Study (CASS) medical registry in an era dominated by coronary artery bypass surgery (CABG). Twelve-year survival rates were 91, 74, 59 and 50% in patients with no-, single-, double- and triple-vessel disease respectively, with even poorer survival rates in patients with the combination of double- or triple-vessel disease and left main stem involvement [3-5].

Table 1. Prognostic variables and criteria indicating a high risk of cardiovascular events amongst various noninvasive stress tests.

Modality	Prognostic variables	Criteria for high risk of CV events	Annual mean CV event rate in normal test
Echocardiography	LVEF at rest LVEF on exercise	LVEF < 35% at rest LVEF < 35% on exercise	
Stress echocardiography	Number of resting WMA Number of inducible WMA with stress	WMA (involving > 2 segments) developing at: A low dose of dobutamine (≤ 10 mg/kg/min) or A low heart rate (< 120 beats/min) Stress echocardiographic evidence of extensive ischemia	< 0.5% [17]
Exercise testing	Exercise-induced angina Exercise capacity BP response to exercise Changes in ST segment Exercise induced ischemia	High-risk Duke treadmill score (< -10)*	Low Duke score (> 4) 0.25% (annual mortality)
Myocardial perfusion imaging	Large stress induced perfusion defects Defects in multiple coronary arteries Transient post stress LV dilation Lung uptake with Tl-201	Stress-induced: Larger perfusion defect (particularly if anterior) Multiple perfusion defects of moderate size Moderate perfusion defect with LV dilation or increased lung uptake (Tl-201) Large, fixed perfusion defect with LV dilation or increased lung uptake (Tl-201)	0.7% [93]

*The Duke treadmill score equals the exercise time in minutes minus (5 × the ST-segment deviation, during or after exercise, in millimeters) minus (4 × the angina index, which has a value of '0' if there is no angina, '1' if angina occurs, and '2' if angina is the reason for stopping the test) [94].
BP: blood pressure; LVEF: Left-ventricular ejection fraction; Tl-201: Thallium 201; WMA: wall motion abnormality.

2.1.3 The SYNTAX score

The SYNTAX score (SXscore) [6] is a tool that can be used to quantify cumulatively the extent and complexity of angiographic CAD. It has been developed from the Leaman score [7] and therefore takes into account not only the number of lesions, their location and characteristics but also the extent of the myocardium subserved. The utility of such scoring system has been shown in the SYNTAX trial [8]. Major adverse cardiovascular and cerebrovascular events (MACCE) rates at 2 years were not significantly different for patients with a low (0 – 22) or intermediate (23 – 32) baseline SXscore treated with either percutaneous coronary intervention (PCI) or CABG; for patients with high SXscores (≥ 33), MACCE continued to be increased at 2 years in patients treated with PCI compared with CABG [9].

2.1.4 Fractional flow reserve in patients with angiographically significant CAD

Patients with coronary lesions showing angiographic stenosis of > 50%, but which are shown to be nonfunctionally significant with an FFR of ≥ 0.75, can have their treatment safely deferred. This has been indicated by the long-term results of the DEFER study, which reported the absence of any significant difference in events at 5 years' follow-up in patients with such lesions (FFR ≥ 0.75), randomized to immediate PCI or medical treatment alone [1]. The subsequent FAME (fractional flow reserve versus angiography for multivessel evaluation) study compared treatment of symptomatic patients with multivessel disease in at least two major epicardial arteries based on using an FFR guide approach or angiography alone. The patient cohort included patients with stable CAD and acute coronary syndrome but not ST-elevation myocardial infarction (STEMI). All angiographic lesions > 50% were treated in the angiography-alone-guided arm, while in the FFR-guided arm, PCI was only done in lesions with an FFR of < 0.80. FFR-guided treatment resulted in fewer deaths, nonfatal myocardial infarctions and repeat revascularizations at 1 year [10]. At 2 years, rates of mortality or myocardial infarction were 12.9% in the angiography-alone-guided group and 8.4% in the FFR-guided group (p = 0.02) [11].

3. Medical treatment versus revascularization

Clinicians often hesitate when it comes to decision making regarding the need of revascularization and the optimal timing for referring a patient for intervention. There are numerous randomized trials comparing medical treatment to revascularization; however, advances in both pharmaceutical and technological fields necessitate the need for recurrent contemporary studies that can guide treatment of CAD today. Of note, some of the major trials comparing medical treatment to revascularization have low or even no use of clopidogrel, and statins, whilst angiotensin converting enzyme (ACE) inhibitor use is often unspecified. In addition, PCI arms in these trials include only treatment with simple balloon angioplasty or

bare metal stents (BMS). The majority of PCI procedures today involve implantation of a stent, and particularly in stable CAD patients this is most commonly a drug-eluting stent (DES). Pivotal trials have established the superior efficacy of DES over BMS in this population [12,13]. Moreover not all DESs have the same safety and efficacy profile as demonstrated in contemporary head-to-head trials [14,15]. (A comprehensive review on current issues with DES has been recently published [16].) Also on the surgical side, CABG was done predominantly using saphenous vein grafts, whereas arterial grafts are commonly employed today. Thus, both medical and revascularization arms of these studies would be considered wholly suboptimal compared with current practice, and this must be considered when interpreting subsequent results. **Table 2** summarizes the components of optimal medical treatment. This is achieved by use of preventive medication, which aims to reduce adverse cardiovascular events, including aspirin, statins, beta-blockers and ACE inhibitors as well as anti-anginal medications (nitrates, beta-blockers, ivabradine, calcium channel antagonists, trimetazidine, ranolazine and nicorandil), which include combination treatment to achieve a therapeutic target as recommended by the European Society of Cardiology (ESC), the American College of Cardiology (ACC) and the American Heart Association (AHA) [17,18]. The efficacy of revascularization in patients with angina after infarction is proven and widely accepted [19]. What is still in question, however, is whether patients with mild or no symptoms, and objective evidence of significant ischemia benefit – in terms of long-term symptom and event-free survival – from early revascularization.

The largest study so far focusing on this question is the COURAGE (clinical outcomes utilizing revascularization and aggressive drug evaluation) trial [20], which randomized 2287 patients with CAD to an initial treatment strategy of PCI and optimal medical therapy (OMT), or OMT alone. Eligible patients had significant CAD and objective evidence of ischemia, but not necessarily angina. Thirty per cent of patients had single-vessel disease, while 40 and 30% had two- and three-vessel disease, respectively. Patients were followed up to a median of 4.6 years with the primary end point of all-cause mortality and nonfatal myocardial infarction. Analysis was done on an intention-to-treat basis allowing crossover. There were no significant differences between groups in mortality (PCI 8.3% vs OMT 7.6%; HR = 0.87, 95% CI 0.65 – 1.16, p = 0.38) or in rates of myocardial infarction(13.2 and 12.3%, respectively; HR = 1.13, 95% CI 0.89 – 1.43, p = 0.33). A fifth of patients undergoing PCI required re-intervention and a third of patients in the OMT group required revascularization during follow-up. The authors concluded that initial management strategy with PCI in patients with stable CAD did not reduce adverse cardiovascular events when added to OMT. The lack of benefit in terms of myocardial infarction and death with PCI over OMT shown in this trial can be attributed to a number of key issues. Importantly, patients enrolled were low-risk patients, which intuitively favors medical treatment. Certainly in a trial setting the compliance of patients to medical treatment is by far better than that seen in real-life clinical practice. In fact, quality-of-life measures including the number of medications and angina-free periods were both dramatically reduced with PCI compared with OMT. A crossover rate in excess of 33% from the OMT group is substantial, and in real terms such a strategy would necessitate close follow-up and repeated readmissions for these patients, something not easily achievable in the real world. Thus, identification of the patient subset in whom OMT is more likely to fail seems ideal. Higher-risk patients with recent onset (within 2 months) CCS class III angina or recent acute coronary syndrome in fact had a higher rate of crossover to revascularization [21]. The number of spontaneous myocardial infarctions in the COURAGE trial was less in the PCI arm (119 vs 108), which did not result in any significantly different outcomes between the two treatment groups. Peri-procedural myocardial infarction in the revascularization arm (n = 35) which intuitively occur more commonly in diffusely diseased coronary arteries with complex anatomies (and high SXscores) [22] also did not tip the balance in favor of the OMT group. Perhaps more importantly, the stents used in the trial were predominantly BMSs; if drug-eluting stents (DESs) had been used instead, this would have most probably decreased the rate of repeat revascularization (21%), and may have extended the quality of life improvement beyond 36 months; but whether it would have affected the hard end points is debatable. Interestingly, the nuclear substudy of the same trial, which included 314 nonrandom consecutive patients, showed a higher ischemia reduction (defined as ≥ 5% reduction in ischemic myocardium on stress myocardial perfusion single photon emission computed tomography) in the PCI group than in the OMT group (33 vs 19%, p = 0.0004) [23]. The difference in ischemia reduction was even more evident in the subgroup of patients with moderate to severe ischemia at baseline (78 vs 52%, p = 0.0007). Patients treated with PCI in this substudy also had more improvement in angina symptoms. The amount of ischemia reduction was proportional to survival. Unfortunately the study was not powered to study outcome differences, but it added weight to the possible superiority of PCI over OMT alone in patients with moderate to severe ischemia at baseline.

A second trial investigating a similar issue is the BARI-2D trial (bypass angioplasty revascularization investigation type-2 diabetes) [24]. The study enrolled 2368 patients with type 2 diabetes mellitus and stable CAD (documented by angina of CCS class I – II in 82% of patients, a positive stress test, and coronary anatomy suitable for PCI or CABG) who were randomly assigned to revascularization with PCI or CABG (revascularization modality was selected at the treating physician's discretion) combined with OMT, or OMT alone. Patients in need of immediate revascularization, or those with left main disease, dyspnea of New York Heart Association (NYHA) class III or greater or previous PCI or CABG within

Table 2. Optimal medical treatment consists of a titrated combination of one or more of the agents listed.

Pharmacological agent	Anti-ischemic effect	Prognostic benefit
Aspirin		MI, stroke and cardiovascular death [95]
Beta-blockers	Decrease in myocardial oxygen demand by lowering inotropy and chronotropy and increasing oxygen supply by increased diastolic coronary filling time	MI, death in patients with previous MI
Nitrates	Increase myocardial oxygen supply by coronary vasodilation and decrease in myocardial oxygen demand by decreasing preload and afterload through vasodilatatory effect	None
Calcium channel blockers	Reduce myocardial oxygen demand by lowering afterload (some also by decreasing inotropy) and increase myocardial oxygen supply though coronary vasodilatation (some by increased coronary diastolic filling time)	None
Trimetazidine	Improved myocardial glucose use through inhibition of fatty acid metabolism	None
Ranolazine	Alters transcellular sodium current resulting in a reduction in intracellular calcium	None [96]
Nicorandil	Potassium channel activation that leads to both arterial and venous vasodilatation by dephosphorylation of the myosin light chain	Decreased MI, mortality [97]
Ivabradine	Selectively inhibits I_f resulting in reduced chronotropy, thereby decreasing myocardial oxygen demand and increases supply through prolonged diastole	Reduction in MI in patients with left ventricular dysfunction and heart rate above 70 despite medical treatment [98]
ACE inhibitors/ARBs		Reduction in MI, cardiovascular death, stroke [99]
Statins	None	Reduction in MI, cardiac mortality, mortality, stroke and revascularization [100-102]

ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker; MI: Myocardial infarction.

the year before enrolment were excluded. At 5 years, there were no significant differences between treatment groups in the primary end point of all-cause mortality (HR = 0.5, 95% CI -2.0 – 3.1; p = 0·97), or in rates of myocardial infarction or stroke. Interestingly, 42% of patients who were assigned to OMT crossed over to revascularization. Of note, patients undergoing CABG rather than PCI (selected according to treating physician's discretion) were a higher-risk group, and analysis demonstrated a significant reduction in nonfatal myocardial infarction after CABG compared with medical therapy alone, whereas no difference was seen between patients undergoing PCI compared with OMT. Disappointingly, the percentage of DES use was low at 35%, as was the prescription of thienopyridines (21%). The authors appropriately concluded that rates of death and major adverse cardiac events did not differ significantly between patients treated by PCI or CABG and those receiving OMT; however, the rates of follow-up revascularizations were increased in the OMT group. Furthermore, patients with the most complex CAD, who were ultimately treated by CABG, had a greater benefit from early revascularization.

In addition to COURAGE and BARI-2D, several other studies have compared revascularization with OMT, and these include RITA-2, TIME, MASS-II and SWISS-II (**Table 3**) [19,25-32].

- The RITA-2 (randomized intervention treatment of angina – second) trial randomized 1018 patients hospitalized for stable or unstable angina and CAD suitable for PCI or medical treatment [25]. Patients with ongoing

Table 3. Randomized trials comparing optimal medical treatment and revascularization for *de novo* coronary artery disease.

	RITA-2 [25-27]	TIME [28-30]	MASS-II [31,32]	SWISS-II [19]	BARI-2D [24]	COURAGE [20]
Number of patients	1018	301	611	201	2368	2287
Angina class (CCS)	0 – III	II – IV	II – III	0	0-II	0 – III
Stress ischemia	90%	69%	100%	100%	–	–
Major inclusion criteria	–	Age > 75	Proximal 2 – 3VD or documented ischemia	Previous MI, silent ischemia	Diabetes	–
Point of randomization	Angiography	Clinical	Angiography	Angiography	Angiography	Angiography
Revascularization type	PCI	PCI/CABG	PCI/CABG	PCI	PCI/CABG	PCI
Stent use	8%	44%	68%	0%	91%	90%
Follow-up (years)	7	4.1	5	10	4.6	5
Crossover rate*	43%	46%	8%	–	38%	30%
Mortality/year	2.6%	5.8%	3.2%	2.1%	1.7%	2.4%

*Crossover indicates the percentage of patients first randomized to optimal medical treatment and subsequently needing revascularization during the period of follow-up.

CABG: Coronary artery bypass graft surgery; CCS: Canadian Cardiovascular Society classification of angina severity; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

instability and those with previous revascularization or left main disease were excluded. Peri-procedural myocardial infarctions in patients treated with PCI contributed to the worse outcome (death/myocardial infarction composite) in this group at 2.7 years (6.7 vs 3.3%, p = 0.02) [27]. In addition, at 7 years' follow-up, although cardiac death was similar between groups, the greatest symptomatic improvement, which was most notably in those with severe symptoms, was seen in the PCI group [27]. With a mere 8% stent use, this study hardly represents contemporary PCI; however, the lessons learned from it continued to be echoed in subsequent studies.

- The TIME study (trial of invasive versus medical therapy in elderly patients) was designed to assess the benefit of PCI in patients aged > 75 years [28]. Three hundred and one patients with chronic stable angina, despite use of at least two anti-anginal tablets, were assigned to either optimization of medical therapy or an invasive strategy consisting of coronary angiography with a view to revascularization. In the invasive group, 79 patients underwent PCI, 30 had CABG, while 43 remained on medical treatment. At 6 months the greatest improvement in angina severity and quality of life was seen in the invasively managed patients. In fact, anti-anginal drugs could be reduced in the invasively managed patients for up to 1 year. Moreover, the need for more revascularizations in the OMT group (46% in the first year) led to a higher major adverse cardiac events (MACE) rate. At 1-year follow-up these revascularizations in the OMT led to an improvement in symptomatic status and in measures of quality of life abolishing the advantage of the invasive strategy [29]. At 4 years, patients who had been revascularized within the first year of the study had a significantly better survival than those receiving drug therapy (76 vs 46%, p = 0.0027) [30].
- The MASS-II (medicine, angioplasty or surgery for multi-vessel disease) study evaluated the effectiveness of the three treatment strategies in 611 patients with stable angina with proven ischemia, good left ventricular function and proximal multi-vessel disease [31]. The superiority of CABG over the PCI and OMT appeared at 1 year with a higher rate of angina-free patients (88% in CABG, 79% in PCI, 46% OMT, p < 0.0001). After 5 years, the primary end point (cardiac mortality, Q-wave myocardial infarction, or refractory angina needing revascularization) occurred in 21% of patients assigned to CABG, 33% to PCI, and 36% to pharmacological therapy (p = 0.0026). There was no difference in survival between the three groups. Thus OMT and PCI were associated with similar rates of adverse events (including revascularization); however, only 55% of patients given drug therapy were free of angina after 5 years, compared with 74% after CABG and 77% after PCI therapy (p < 0.001) [32].
- The SWISS-II trial (Swiss interventional study on silent ischemia type II) studied patients with silent ischemia 3 months post-myocardial infarction. PCI in this population decreased both the rate of detectable ischemia as well as resulting in a better MACE (cardiac death, myocardial infarction or symptom driven revascularization)-free survival compared with medical treatment alone [19].
- In addition to these randomized studies, several meta-analyses have also been done comparing revascularization with OMT, with conflicting results. Jeremias *et al.* performed a meta-analysis of more than 13,000 patients with stable CAD treated with OMT or revascularization (17 with PCI; 6 with CABG; 5 PCI or CABG) and showed that mortality rates were lower in revascularization groups, which was most notable in those studies in which CABG was the revascularization modality in

use: CABG versus OMT (OR = 0.62, 95% CI 0.50 – 0.77), PCI versus OMT (OR = 0.77, 95% CI 0.65 – 0.91) [33]. Similarly, a meta-analysis by Schomig *et al.* which included 17 studies reported a 20% reduction in mortality following PCI compared with OMT [34]. It should be noted that the population included was not representative of patients with *de novo* coronary lesions since, amongst other flaws in this study, post-myocardial infarction patients were included. Moreover, many of the studies were conducted in the 1980s and therefore do not represent an assessment of contemporary treatment. In contrast to these two meta-analysis, a more recent study of PCI versus medical therapy, which included more than 25,000 patients, failed to demonstrate superiority of either treatment [35]. Specifically the risk ratio for indirect comparisons between DES and medical therapy was 0.96 (95% CI 0.60 – 1.52) for death and 1.15 (0.73 – 1.82) for myocardial infarction. The heterogeneity in patients and treatment modality is a plausible reason for the discrepancies between the trials and meta-analyses. It is reasonable, therefore, to conclude that certain patient groups, such as those with documented ischemia, those with multi-vessel disease including left main disease and those revascularized by CABG, are more likely to obtain a survival benefit from revascularization compared with other groups.

4. PCI versus CABG for revascularization

In those patients in whom revascularization has been deemed appropriate, a decision needs to be made regarding whether this should be done using PCI or CABG. Although both revascularization strategies have a common aim, which is to restore adequate flow to the myocardium supplied by a diseased coronary artery, they differ completely in their approach. PCI involves implantation of stents, most commonly in the proximal coronary vessel, treating the existing lesion. On the other hand, bypass grafts are placed in the mid coronary vessel, thereby not only treating the culprit lesions but additionally providing prophylaxis against the development of '*de novo*' proximal CAD. Thus procedural risks, long-term safety and efficacy are expectedly different.

The discussion regarding whether to perform PCI or CABG has evolved dramatically since the start of PCI in 1978 [36]. This evolution, which has been fuelled by technological advances such as new coronary guidewires, the introduction of coronary stents (in particular DES), and new antiplatelet agents, has led to changes in the thresholds by which patients are referred for PCI or CABG.

4.1 Single-vessel disease

Revascularization for single-vessel disease (SVD) carries a significantly lower mortality compared with those having multi-vessel disease (MVD). Early trials of revascularization showed a distinct advantage for CABG compared with medical therapy in patients with a significant proximal left anterior descending artery (LAD) lesion [37]. In addition, evidence from large registries such as the New York state registry and the Duke registry have indicated that CABG also offers a significant survival advantage over PCI in these specific patients [38,39]. In fact, the commonest indication for CABG in patients with SVD in the aforementioned registry was a lesion in the proximal LAD [39].

As alluded to earlier, study results must be interpreted after considering the PCI and surgical techniques used to treat the patient population, and it is therefore of great relevance that stent usage in the New York registry was only 11.8%. With respect to bypass conduits, rates of arterial graft use were not stated; however, the time period when the studies were conducted (Duke registry 1984 – 1990; New York registry 1993 – 1995) would certainly indicate that rates of arterial grafts, particularly to the LAD, were likely to be lower than in contemporary practice.

More contemporary data are derived from two meta-analyses examining outcomes in patients with proximal LAD disease randomized to either PCI or CABG. Kapoor *et al.* concentrated on any surgical technique [40], whilst Aziz *et al.* examined specifically those having the minimally invasive direct coronary artery bypass (MIDCAB) [41]. Notably, the use of stents and left internal mammary artery (LIMA) grafts were much higher than documented in the previously mentioned registries. Results from both studies showed that no significant difference in survival, and significantly lower rates of repeat revascularization after CABG; with results maintained up to 5 years' follow-up in Kapoor's study. The excellent long-term prognosis of both treatments is further supported by Goy *et al.*, who reported no significant differences in mortality up to 10 years' follow-up among 123 patients with proximal LAD lesions randomized to CABG with a LIMA graft or PCI with a BMS [42].

In patients with SVD not involving the proximal LAD, the default method of revascularization is PCI. In those patients with proximal LAD disease, while historically CABG was the preferred treatment, evidence now suggests that PCI offers a similar survival benefit (up to 10 years), and therefore is a viable alternative.

4.2 Multi-vessel disease

Several randomized, as well as nonrandomized trials have compared the safety and efficacy of PCI and CABG amongst patients with MVD eligible for both treatments.

4.2.1 PCI with bare metal stent versus CABG

The randomized studies comparing PCI with BMS versus CABG in patients with MVD include:

- The ARTS-I (arterial revascularization therapies study I) trial randomized 1205 patients with stable and unstable angina, who had at least two *de novo* lesions in two

major coronary arteries, to treatment with CABG or stenting with the Crown or Coroflex BMS [43-45]. At 5 years no significant differences were seen in rates of mortality, myocardial infarction and stroke between the two groups. Overall the MACCE rate was significantly higher in the PCI group (41.7 vs 21.8%, p < 0.001), which was driven by an increased need for repeat revascularization with PCI ((RR = 3.27, CI 2.3 – 4.65, by PCI and 7.92, CI 3.64 – 17.3, by CABG) [45].

- The ERACI-II trial enrolled 450 patients with MVD and demonstrated a lower rate of mortality and myocardial infarction with BMS compared with CABG at 1- and 18-month follow-up [46]. This advantage with PCI disappeared at 5-year follow-up, such that results reflected those of similar studies with comparable safety between both strategies and better efficacy with CABG [47].
- The SoS (stent or surgery) trial that randomized 988 patients is the only study of its type to show a continuing survival advantage of CABG over PCI (HR = 1.66, 95% CI 1.08 – 2.55, p = 0.022) up to a median of 6 years' follow-up [48,49].
- The MASS-II study mentioned earlier, added a third comparator, medical treatment, to assess outcomes in 611 patients with MVD and preserved left ventricular function, who were randomly assigned to undergo CABG (n = 203), PCI (n = 205), or have OMT (n = 203) [31]. At the 5-year follow-up no differences were observed in overall mortality among the three groups. In addition, 9.4% of OMT and 11.2% of PCI patients underwent repeat revascularization procedures compared with 3.9% of CABG patients (p = 0.02). Moreover, 15.3, 11.2 and 8.3% of patients experienced a nonfatal myocardial infarction in the OMT, PCI and CABG groups, respectively (p < 0.001). The pairwise treatment comparisons of the primary end points showed no difference between PCI and OMT (RR = 0.93, 95% CI 0.67 – 1.30) and a significant protective effect of CABG compared with OMT (RR = 0.53, 95% CI 0.36 – 0.77). All three treatment regimens yielded comparable, relatively low rates of death. OMT was associated with similar incidence of long-term events, and the rate of additional revascularization was not different from that in the PCI group.

Meta-analysis of randomized controlled trials comparing PCI with BMS and CABG in patients with MVD, found only minimal survival benefit in the CABG arm with survival benefits shown only in specific subgroups. However a striking fivefold reduction in repeat intervention was seen in the CABG-treated patients [50-52]. In a pooled patient level meta-analysis of these four major randomized studies, namely the ARTS, ERACI-II, MASS-II and SoS trials that cumulatively enrolled 3051 patients and reached 5 years of follow-up, Daemen *et al.* confirmed the equivalence of PCI and CABG with respect to safety outcomes (16.7 vs 16.9%, respectively; HR = 1.04, 95% CI 0.86 – 1.27; p = 0.69). Again efficacy was better with CABG owing to lower rates of repeat revascularization (29.0 vs 7.9%; HR = 0.23, 95% CI 0.18 – 0.29; p < 0.001) (**Figure 1**). No heterogeneity of treatment effect was found in the subgroups, including diabetic patients and those presenting with three-vessel disease [51].

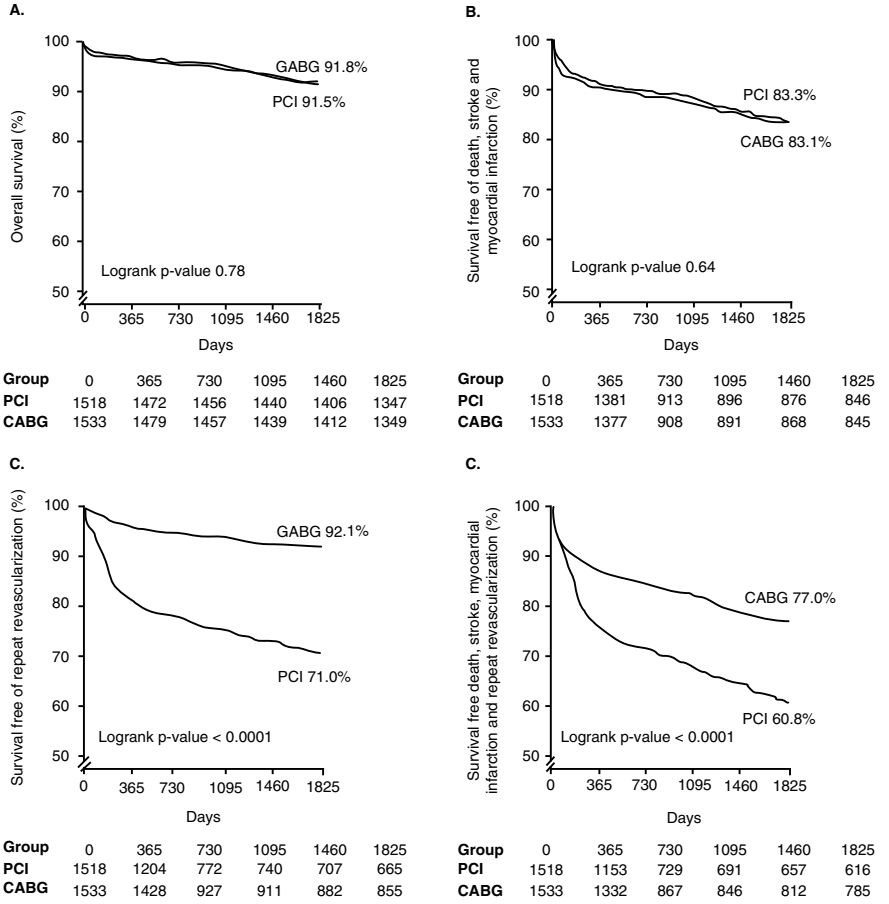
Additional data come from an individual patient pooled analysis of 10 randomized studies, which included 7812 patients, and reported a similar mortality rate between the two treatment modalities (CABG, 15%; PCI, 16%) at a median follow-up time of 5.9 years. In a diabetic subgroup of 1223 patients, the rate of mortality was significantly lower with CABG (HR = 0.70, 95% CI 0.56 – 0.87; p = 0.014) [52]. Similarly, the survival was better with CABG in older patients, achieving a hazard ratio of 0.82 (95% CI 0.70 – 0.97) for those aged over 65 years. Moreover, the prespecified composite of death or repeat intervention was significantly lower in CABG (9.9 vs 24.5%, p < 0.001). In this meta-analysis, however, simple balloon angioplasty was the default PCI procedure in six trials, limiting the extrapolation of the results to the stent era.

4.2.2 PCI with drug-eluting stent versus CABG

The introduction of DES represents an important revolution in the revascularization of coronary lesions. The first DES, the sirolimus-eluting Cypher stent (Cordis Corp, Warren, NJ, USA) was available commercially in Europe as from April 2002 and in the USA in 2003 [53]. This was closely followed by the TAXUS paclitaxel-eluting stent (PES; Boston Scientific, Natick, MA, USA). The dramatic reduction in the rate of repeat revascularization seen in the first randomized trials against BMS drove the widespread use of DES in the real world [12,13]. In fact, complex lesions including bifurcation lesions, long lesions, left main stem lesions and MVD no longer represented a taboo for PCI, and registries pictured the unlimited use of the noninvasive interventions in patients who were classically surgical candidates [53].

The air of positivity with DES instigated investigators to compare this new technology with CABG. The ARTS-II study was designed to compare clinical outcomes, safety and efficacy of the sirolimus-eluting stent (SES) with the historical outcomes of CABG and BMS from the ARTS-I [54]. Six hundred and seven patients with two- and three-vessel disease were studied. At 5 years, SES had a safety record comparable to CABG with death/stroke/myocardial infarction event-free survival rates of 87.1% for SES, versus CABG 86.0% (p = 0.1), and superior to BMS 81.9% (p = 0.007) [55]. However the MACCE rate with SES was higher than in patients treated with CABG, and lower than in those treated with BMS; with rates of repeat revascularization the major driving force behind these differences (**Figure 2**).

Similarly, the ERACI-III prospectively added a 205 patient cohort treated with DES and compared them with historical



Group	0	365	730	1095	1460	1825
PCI	1518	1472	1456	1440	1406	1347
CABG	1533	1479	1457	1439	1412	1349

Group	0	365	730	1095	1460	1825
PCI	1518	1381	913	896	876	846
CABG	1533	1377	908	891	868	845

Group	0	365	730	1095	1460	1825
PCI	1518	1204	772	740	707	665
CABG	1533	1428	927	911	882	855

Group	0	365	730	1095	1460	1825
PCI	1518	1153	729	691	657	616
CABG	1533	1332	867	846	812	785

Figure 1. Long-term clinical outcomes from a patient-level pooled analysis of 3051 patients who were randomized to percutaneous coronary intervention using bare metal stents or coronary artery bypass grafting. Kaplan–Meier event-free survival analysis of death **A**; death, stroke, or myocardial infarction **B**; repeat revascularization **C**; and major adverse cardiac and cerebrovascular events (death, stroke, myocardial infarction and repeat revascularization **D**.

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cohorts of BMS versus CABG from the ERACI-II study [56]. At 3 years, MACCE was lower in ERACI-III–DES (22.7%) than in ERACI-II–BMS (29.8%, p = 0.015), mainly owing to less target vessel revascularization (14.2 vs 24.4%, p = 0.009). The initial advantage for PCI with DES over CABG observed at 1 year (MACCE rate 12 vs 19.6%, p = 0.038) was lost by 3 years (both 22.7%, p = 1.0).

In addition to these studies, the largest body of evidence to guide our practice so far in the DES-dominated era, comes from two randomized trials: SYNTAX and CARDia [8,57,58].

The SYNTAX trial (synergy between percutaneous coronary intervention with taxus and cardiac surgery) enrolled 1800 patients with three-vessel and/or left main CAD who were randomized to PCI or CABG, and also included a

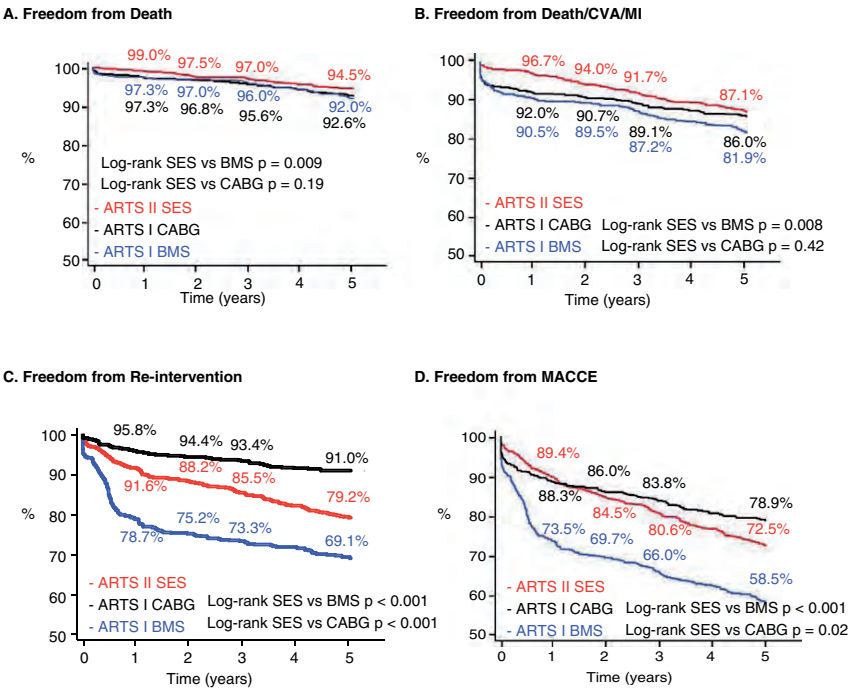

Figure 2. Long-term clinical outcomes between patients treated with drug-eluting stents (ARTS-II SES), bare metal stents (BMS) and coronary artery bypass surgery (CABG) in the Arterial Revascularization Therapy Studies I and II [45,55]. Kaplan–Meier estimates for freedom from death **A**, death/myocardial infarction/stroke **B**, repeat revascularization **C**, and overall major adverse cardiovascular and cerebrovascular events (MACCE) **D**.

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parallel 1275 patient registry consisting of 1077 CABG patients unsuitable for PCI and 198 PCI patients with excessive surgical risk [8]. The TAXUS PES was used exclusively in the PCI arm. At 2 years, 16% of CABG and 23% of PCI patients reached the primary composite of death, myocardial infarction, repeat revascularization and stroke ($p < 0.001$). This was largely driven by lower repeat revascularization in the CABG group (8.6 vs 17.4%, $p < 0.001$). The incidence of stroke was higher in the CABG patients (2.8 vs 1.4%, $p = 0.03$), while myocardial infarction occurred more frequently in the PCI patients (3.3 vs 5.9%, $p = 0.01$). No difference was observed in the death and safety composite of death/stroke/myocardial infarction [9].

In a patient subgroup with three-vessel disease (CABG, n = 549; PCI, n = 546) patients treated by CABG had lower rates of myocardial infarction, cardiac death and repeat revascularization. There was also a trend for higher rates of stroke with CABG; however, in this subgroup overall MACCE still favored surgical revascularization (14.4 vs 23.8%; $p < 0.001$). Additional analysis of these patients, taking into consideration the complexity of their disease using the SXscore, enabled more definitive conclusions to be reached regarding the most appropriate mode of revascularization. In patients with SXscores in the lowest tertile (0 – 22), a similar rate of overall MACCE was seen between PCI and CABG; whilst in patients with SXscores above 22, rates of MACCE were significantly higher with PCI (**Figure** 3). Thus patients with triple-vessel disease and SXscores in the higher two tertiles should ideally be treated with CABG. These results echoed those of the first-year follow-up, and, while keeping in mind that subgroup analysis in SXscore tertiles compared a relatively small number of patients (150 – 200), disease extent and severity should influence our choice of the best treatment strategy for patients amenable to both types of intervention.

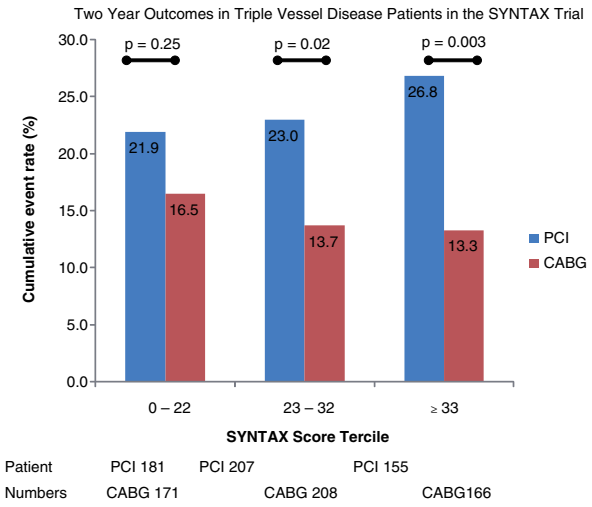

Figure 3. The rates of MACCE (death, stroke, myocardial infarction and repeat revascularization) at 2-year follow-up amongst patients with triple vessel disease treated with percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) in the SYNTAX trial.

For patients with a SYNTAX score between 0 and 22 PCI offers a suitable alternative to CABG [92].

The optimal management of MVD in patients with diabetes has been the focus of the CARDia (coronary artery revascularization in diabetes) trial [58]. This noninferiority trial randomized 510 diabetic patients with proximal LAD stenosis or MVD to either PCI or CABG. The Cypher stents were used in 69% of cases with the rest being BMS. At 1 year, the safety composite end point (mortality, myocardial infarction, nonfatal stroke) was similar in both groups, however, patients undergoing CABG required less repeat revascularization at 1 year (2.0 vs 11.8%) Patients with CABG also had significantly less angina. Repeat revascularization rates were lower with the DES *post hoc* subgroup such that the composite of mortality, myocardial infarction, stroke and repeat revascularization was not different between PCI with DES and CABG (12.4 vs 11.6%, HR = 0.93, 95% CI 0.51 – 1.71; p = 0.82). These results, however, can only be regarded as hypothesis generating and are by no means definitive as the trial was underpowered to detect differences between these treatment groups following the failure to recruit the required 600 patients.

These studies comparing PCI with CABG have some notable major limitations. Ethically, all patients who were enrolled were required to have disease suitable for treatment by PCI or CABG, thereby preventing the randomization of a patient to PCI who had disease that could not be treated adequately. Importantly, these patients are most likely to gain prognostically from CABG and, therefore, the lack of survival advantage with CABG in the previous randomized, controlled trials is probably no surprise. In addition, screening of patients resulted in < 5% of patients being enrolled, with common exclusion criteria: ostial LAD, impaired left ventricular function and left main disease – all lesions/patient types who gain most from CABG. Finally, percutaneous therapy was via plain old balloon angioplasty (POBA) and BMS and therefore not contemporary. The SYNTAX trial addressed some of these limitations by removing specific inclusion/exclusion criteria, but patients were still required to have disease amendable to both treatments; 70% of screened patients were enrolled.

4.2.3 *Completeness of revascularization*

Successful revascularization of all angiographically significant lesions (> 50% diameter stenosis) in vessels with a reference diameter of ≥ 1.5 mm is more common with CABG than with PCI [59]. This is most commonly due to unsuccessful PCI treatment of complex lesions with characteristics including heavy calcification, and a total occlusion. These patients are more likely to require a second revascularization intervention (often a bypass grafting). Moreover, incomplete revascularization with PCI in the stent era, although more common in patients with comorbid conditions such as poor left ventricular function, renal disease and stroke, is associated with a higher mortality rate at follow-up compared with complete revascularization [60].

5. Specific patient and lesion subsets

5.1 Specific patient subsets

5.1.1 Diabetic patients

Diabetic patients represent 20% of all patients with CAD [61], which often presents late due to silent myocardial ischemia with extensive complex disease and has a rapid clinical course. Moreover, the risk of myocardial infarction in diabetics is much higher than in the rest of the population (3.5 vs 20.2%, $p < 0.001$) [62]. This is also true for other major adverse cardiovascular events. Therefore, aggressive blood glucose control to achieve levels of HbA1c of < 7% as well as lifestyle and pharmacological treatment targeted at other associated risk factors (hypertension, hypercholesterolemia) is a crucial first step. The need for revascularization as in other patients should be based on symptoms, degree of ischemia and coronary disease involvement. The poorer performance of revascularization strategies compared with the nondiabetic population stems mainly from the nature of the disease. In fact, long-term survival in diabetics is worse both with PCI and CABG [63,64]. As discussed earlier, results from the BARI-2D study revealed no difference in rates of death and major adverse cardiovascular events in diabetic patients randomized to revascularization (by PCI with BMS or CABG) or OMT for up to 5 years of follow-up. However, in patients with extensive disease CABG is recommended as a significant difference in MACE rate of 22.4 versus 30.5% was observed in a subgroup of CABG versus OMT in the same study [24]. The CARDia trial recently also added proof to the superiority of CABG over PCI with BMS. However, as noted earlier, the end points were not different on subanalysis of DES versus CABG [58]. This observation is to some extent heralded by earlier studies (both randomized and real-world registries) that have shown better outcomes in terms of efficacy of the sirolimus-eluting Cypher stent compared with BMS [65-68]. The SCORPIUS randomized study showed a remarkably lower in-segment late luminal loss of 0.18 mm in the SES group (n = 98) compared with 0.74 mm in the BMS group (n = 102), reflecting in a target lesion revascularization (TLR) rate favoring the DES (3 vs 25%, $p < 0.001$) at 1 year [66]. Similarly, the DIABETES trial showed a significantly lower TLR rate at 2 years (8 vs 35%, $p < 0.0001$) in 78 diabetic patients randomized to SES compared with that in 80 diabetic patients receiving BMS. This again was the only significant contributor to a difference in MACE (12.8 vs 41.3%, $p < 0.0001$). In the SCAAR registry, the re-stenosis rate in diabetic subjects receiving DES was halved as compared to BMS at a median of 2.5 years [68].

Meta-analysis of the first SES and PES randomized trials showed that late lumen loss at 6 – 9 months was 0.93 mm for BMS versus 0.18 mm for DES ($p < 0.001$), which was reflected in a higher re-stenosis rate [69]. SES outperformed PES in terms of efficacy as was shown in an earlier randomized trial of SES versus PES in diabetic patients. In-segment late loss for SES was 0.43 mm as opposed to 0.67 mm with PES ($p = 0.002$). The binary re-stenosis was also lower (6.9 vs 16.5, $p = 0.03$) and there was a trend towards lower target lesion revascularization (6.4 vs 12, $p = 0.13$) [70].

Analysis of the diabetic population (n = 452) in the SYNTAX trial, also revealed equal safety end point events with higher revascularizations in the PES-treated group compared with surgery at 1 year [71]. More clarifications on optimal treatment await the longer-term follow-up of this study as well as the results of the FREEDOM (future revascularization evaluation in patients with diabetes mellitus: optimal management of multivessel disease) trial [72].

5.1.2 Other high-risk patient subsets

Renal insufficiency is associated with increased incidence of diffuse atherosclerosis, especially when it complicates diabetes mellitus. Surgical and percutaneous revascularization in patients with moderate renal insufficiency (creatinine clearance of < 30 ml/min) were comparable with respect to safety end points at 5-year follow-up in an ARTS-I trial subgroup analysis. However, higher target vessel revascularization (TVR) rates in the patients treated percutaneously (18.8 vs 8.2%, $p = 0.08$) made this treatment option less effective than surgical revascularization in this patient group amenable to both treatment options [73]. While DES is more effective than BMS also in renal failure patients, more data from the DES era are needed to provide an updated comparison between contemporary PCI and CABG treatment strategies.

The choice of revascularization for high-risk patients with poor left ventricular function intuitively depends on the balance between surgical risk, risk of percutaneous intervention and the predicted benefit, which may be pre-procedurally evaluated by noninvasive myocardial viability studies.

5.2 Specific lesion subsets

5.2.1 Bifurcations

Bifurcation lesions are a high-risk subset with higher risk of re-stenosis of the sidebranch even with the use of DES [74]. There are no randomized trials to compare surgical and percutaneous intervention of such lesions. In cases treated by interventionalists, the simple provisional T-stenting technique has been consistently shown to be safer and associated with better outcome compared with more complex two-stent techniques [75-79].

5.2.2 Chronic total occlusions

Chronic total occlusions (CTO), which are seen in up to 20% of patients, remain a challenge in today's PCI and are still one of the commonest reasons for referring a patient for CABG. Revascularization of CTOs is beneficial especially in patients with reversible ischemia in the territory supplied by the artery [80]. Advances in techniques such as the retrograde technique, development of dedicated wires and increasing operator experience have increased the PCI procedural success rates to ~ 75% [81]. MSCT may play a role in patient selection for intervention since patients with excessive lesion length,

calcification and tortuosity have a lower likelihood of PCI success and may benefit from a direct referred to surgery [82]. For patients in whom successful recanalization occurs, SES is superior to BMS in terms of less re-stenosis and consequently less need for revascularization [83,84]. A recent meta-analysis including 4394 patients from 14 studies comparing BMS with DES (SES or PES) in CTOs also reported superiority of DES with TVR rates of 11.7% at ≥ 3 years' follow-up, which is comparable to rates seen in 'off-label' use of such stents.

5.2.3 Left main disease

In left main disease, PCI offers similar safety as with CABG with no difference in composite of death, myocardial infarction and stroke. Efficacy is however better with CABG as PCI patients require significantly more repeat interventions. This has been demonstrated by Naik *et al.* [85] in a 10-study meta-analysis in patients followed to 3 years, and similar results have been recently reported for the first-year follow-up of a prespecified left main subgroup analysis from the SYNTAX trial [86]. In this left main subgroup, MACCE rates were similar between PCI and CABG in low SXscore (0 – 22) and intermediate SXscore (22 – 32), whereas in high scores higher MACCE rates were observed in the PCI group, mainly driven by increased revascularizations. These results, which indicate that PCI is a suitable alternative to CABG in patients with left main lesions and a SXscore less than 33, have led to changes in the recommendation for PCI in patients with left main lesions. The 2009 focused update on PCI published by the ACC/AHA upgraded PCI for left main lesions from a class III to a class IIb indication, such that it may be considered in patients whose coronary anatomy is associated with a low risk of procedural complications of treatment by PCI, and/or clinical conditions that predict an increased risk of adverse surgical outcomes [87]. Finally, the EXCEL trial (evaluation of Xience Prime versus coronary artery bypass surgery for effectiveness of left main revascularization), which will randomize 2500 patients with left main lesions and an SXscore of < 33 to treatment with either PCI using the Xience Prime everolimus eluting stent (Abbott Vascular, Santa Clara, CA, USA) or CABG, will provide more definitive information on this important patient subset. The trial aims to commence enrolment in late 2010 [88].

6. Quality-of-life improvement with various coronary lesion treatment options

Relief from or reduced frequency of anginal symptoms, use of fewer anti-anginal medications, reduced need for repeat revascularization and improved exercise capacity are among the most important contributors for an improved quality of life as assessed from a patient's perspective. The COURAGE, RITA-2 and FAME trials showed that revascularization is superior to medical treatment with respect to freedom from angina, especially for patients with the more severe classes of angina. Moreover, one third of patients in the OMT groups required revascularization for symptom relief. DES use has significantly reduced the recurrence of symptoms after PCI with subsequent decline in repeat revascularizations [35].

Analysis from CABG versus PCI studies such as from ARTS-II show that, up to 12 months after procedure, DES patients are better off than patients treated with BMS or CABG. This aspect is gaining more importance as more studies show equivalence in safety and efficacy end points and patient-informed choice may therefore increasingly influence the decision of the preferred revascularization method [89].

7. Cost–benefit of CAD treatment according to treatment modality

The overall cost of a procedure not only depends on its initial cost but also has to take into account additional costs should the treatment fail. Data from the COURAGE trial showed that the addition of PCI to optimal medical therapy was not a cost-effective initial management strategy for symptomatic, chronic CAD [90]. In fact, PCI had an added cost of ~ $10,000, without significant gain in life-years or quality-adjusted life-years. With regard to the revascularization strategies, the BARI trial found that, although initial costs of PCI with BMS were lower than CABG, a higher rate of repeat procedures in the PCI arm eliminated the advantage at 10 – 12 years [91]. Similarly, in ARTS-I, PCI was less expensive at 1 year but lost its advantage because of the need for repeat procedures. A risk–benefit acceptability curve for the same study showed that, typically, a patient has a 0.7 risk of revascularization during a 3-year period after PCI in exchange for being symptom-free for 1 month after the index procedure. More cost–benefit analyses are required in the DES era as procedure costs have changed significantly since these earlier studies.

8. Conclusions

Optimal treatment of *de novo* coronary lesions requires careful assessment and management of patients' risk factors as well as commencement of secondary prevention measures with the aim to limit progression of the disease and to prevent acute events. Documentation and localization of ischemia is ideal, especially in patients whose symptoms are refractory to medical anti-anginal therapy, preferably before they are referred for invasive coronary angiography. The location, extent and complexity and functional importance of CAD and their quantification by tools such as the SYNTAX score and FFR should help the treating physician, interventional cardiologist, cardiac surgeon and patient to proceed with the appropriate revascularization strategy, if this is indicated. Revascularization should be considered in all patients with CAD and documented moderate-to-severe ischemia as an adjunct to medical therapy as it improves symptoms and has prognostic implications in patients with high disease burden. On the other hand, patients

with no or mild symptoms and little ischemia can be treated with medical treatment alone.

9. Expert opinion

Percutaneous coronary intervention has caused a major revolution in the treatment of coronary artery disease. Development in PCI technology during this decade has allowed its widened application, which has expanded from treatment of simple lesions in a single vessel to treatment of complex disease including left main stem lesions and multi-vessel disease. Today PCI has found its place alongside optimal medical treatment and coronary artery bypass surgery as a treatment option for patients with CAD. Understanding the benefits and drawbacks of these treatment strategies is a crucial prerequisite for clinicians to enable them to recommend the optimal management for their patients. Trials and research conducted or published during this decade have taught us some fundamental lessons that must be kept in mind both when applying this knowledge to clinical practice, as well as when designing future clinical trials.

First, the SYNTAX trial has shown that CAD location and complexity rather than mere numeration of vessel involvement help determine the best revascularization option. Thus while patients with low (0 – 22) and intermediate (23 – 32) SXscores have similar MACCE rates with PCI and CABG at 2 years, patients with SXscores of ≥ 33 have higher MACCE rates when treated with PCI.

Second, a clinical evaluation of the patient with particular attention to disease states like diabetes is essential because such patients are at high risk of disease progression. Recent evidence indicates similar safety and efficacy of CABG and PCI with DES.

Although it seems logical, revascularization is beneficial when limited to vessels with significant functional stenosis, as shown in the FAME trial.

Identification of vulnerable plaque, which may be better defined by invasive (IVUS, virtual histology) imaging, may in the future identify patients at higher risk of acute adverse events even in the absence of significant flow-limiting lesions. Medications, especially statins, may have a special role in stabilizing CAD and thereby preventing plaque rupture and its adverse consequences.

Research efforts will continue to define the role of each of the three treatment modalities in coronary lesion and patient subsets. In the meantime, advances across the three fields with development of new stents including the bioabsorbable stents, refinement in minimally invasive surgery and development of new drugs will call for redefinition of their role in the treatment of CAD.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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2.2

Four-year clinical outcome of sirolimus- and paclitaxel-eluting stents compared to bare-metal stents for the percutaneous treatment of stable coronary artery disease.

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Four-Year Clinical Outcome of Sirolimus- and Paclitaxel-Eluting Stents Compared to Bare-Metal Stents for the Percutaneous Treatment of Stable Coronary Artery Disease

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Background: There are limited data on the long-term safety and efficacy profile of coronary stent implantation in patients with stable coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI). Objective: We aimed to assess the 4-year clinical outcome in patients who received a bare-metal stent (BMS), sirolimus-eluting stent (SES), or a paclitaxel-eluting stent (PES) for the percutaneous treatment of stable angina in our center during 2000–2005. Methods: In the study period, a total of 2,449 consecutive patients (BMS = 1,005; SES = 373; and PES = 1071) underwent a PCI as part of three historical PCI-cohorts for stable angina and were routinely followed for the occurrence of major adverse cardiac events (MACE). Results: At 4 years follow-up, 264 BMS patients (26.8%) had a MACE, compared to 75 SES patients (20.9%) and 199 PES patients (23.9%). Multivariate analysis showed that SES and PES were superior to BMS with respect to MACE [hazard ratio (HR) = 0.62, 95% confidence interval (CI): 0.47–0.81; HR = 0.67, 95% CI: 0.55–0.82, respectively]. The occurrence of MACE was significantly lower in the SES and PES population, primarily due to less target-vessel revascularization (TVR) procedures (HR = 0.53, 95% CI: 0.37–0.75; HR = 0.71, 95% CI: 0.62–0.81, respectively). The occurrence of early, late, and very late stent thrombosis was equally rare with each stent type. There were no significant differences between SES and PES on death, myocardial infarction, TVR, and MACE. Conclusion: These findings suggest that SES and PES result in decreased TVR procedures and MACE compared to BMS at 4 years follow-up. SES or PES implantation should be the preferred choice over BMS for patients with stable CAD undergoing PCI.

Key words: stents; percutaneous coronary intervention; stable coronary disease

INTRODUCTION

Several randomized clinical trials suggested that an optimal medical approach, consisting of proper antianginal medication and life-style modifications, might be the preferred initial strategy for patients with stable coronary artery disease (CAD) [1–3]. Still, percutaneous coronary interventions (PCI) are increasingly being performed as a first-line therapeutic option for stable CAD. A recent meta-analysis has shown that PCI resulted in a significant 20% reduction in mortality rates compared to optimal medical treatment for treating stable angina after an average of 51-month follow-

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Conflict of interest: Nothing to report.

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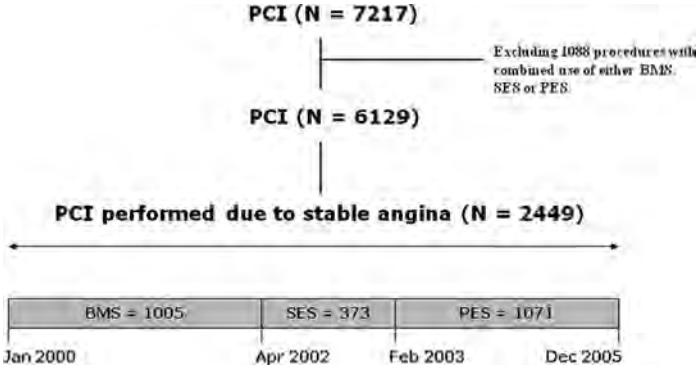

Fig. 1. The three historical cohorts in chronological order. Patients undergoing multiple revascularization procedures were only enrolled in the first original cohort. The combined use of different types of stents in the same procedure resulted in exclusion.

up [4]. In addition, coronary angioplasty resulted in a greater and faster angina relief compared to only medical treatment, especially in patients with Canadian Cardiovascular Society (CCS) classification scores of two or higher [5–7].

By combining the mechanical-scaffolding properties of a conventional bare-metal stent (BMS) with an antiproliferative drug coating, polymer-based drug-eluting stents (DESs) revolutionized angiographic restenosis rates post-PCI [8,9]. Sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) were the first DES that obtained Conformité Européenne mark and Food and Drug Administration approval. Although the mechanisms of cell-cycling inhibition are dissimilar, both have shown a persisting advantage on target-vessel revascularization (TVR) procedures and major adverse cardiac events (MACE) compared to BMS [10–14]. Nevertheless, a recent study showed that patients with stable angina did not have less major adverse cardiac and cerebrovascular events after 36-month post-PCI with the implantation of DES when compared with BMS, due to a higher event rate after the first year [15].

Although DESs have been shown to have a short-term clinical advantage compared to BMS for patients with stable angina, it remains unknown whether this advantage is sustained [16]. By systematically conducting multiple PCI registries, consisting of exclusive use of BMS and DES in consecutive time periods, we are able to assess the differential outcome of these stents. Therefore, the aim of this study was to evaluate prospectively the long-term safety and efficacy profile of the SES, PES, and BMS in patients undergoing PCI for stable angina.

METHODS

Patient Population and Study Design

From January 2000 until December 2005, a total of 7,217 consecutive patients were treated with PCI. The 1,088 patients who received different types of stents during the initial procedure were excluded from the current analysis. In total, 2,449 patients (40%) underwent a PCI for the treatment of stable coronary artery disease for which BMS was used in 1,005 procedures until April 2002 (Fig. 1). As part of the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital registry, 373 procedures were performed using the SES (Cypher®, Cordis Corp., Johnson & Johnson, Warren, NJ) for the treatment of stable coronary disease from April 2002 until February 2003 [17]. The PES (TAXUS™, Express2™, or Liberté™, Boston Scientific, Natick, MA) was used in 1,071 patients with stable angina as the default strategy for all PCI as part of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital registry from February 2003 to December 2005 [18]. In short, both were all-comer single-center registries with the main purpose of evaluating the safety and efficacy of SES and PES implantation. These registries were conducted according the dynamic registry design described by Rothman et al. [19].

All procedures were performed according to standard clinical guidelines, and every patient was pretreated with aspirin and $\geq$300 mg clopidogrel. The post-PCI antiplatelet regimen consisted of $\geq$80 mg aspirin lifelong and $\geq$75 mg clopidogrel for at least 1 month if BMS were used, $\geq$3 months for patients with SES, and $\geq$6 months for patients with PES. Periprocedural glycoprotein IIb/IIIa antagonists were used at the discretion

of the interventional cardiologist. The study protocol was approved by the institutional ethics committee, and all patients provided written informed consent.

Definitions and Clinical Endpoints

Diabetes, subdivided into noninsulin dependent and insulin dependent, was defined as the usage of antidiabetic medication. Blood pressure $\geq$140/90 mHg or the usage of antihypertensive medication was classified as hypertension. Hypercholesterolemia was defined as the usage of lipid lowering drugs or a fasting total cholesterol $\geq$6.2 mmol/l. Procedural success was defined as the successful deployment of the stent and a residual stenosis $<$30% by visual analysis in the presence of thrombolysis in myocardial infarction three flow grade without the occurrence of MACE within 2 days postintervention. Procedural success without the occurrence of death or myocardial infarction (MI) during the index hospitalisation was defined as clinical success.

As recommended by the Academic Research Consortium criteria, definite stent thrombosis was defined as angiographically documented thrombus in or within 5 mm of the stent, accompanied by at least one of the following criteria: (1) acute symptoms; (2) ischemic ECG changes; and (3) typical rise and fall of cardiac markers. The timing of stent thrombosis was categorized into early (within 30 days poststent implantation), late (within 30 days and 1-year poststent implantation), and very late (after 1-year poststent implantation).

Primary end point was the occurrence of MACE [defined as a composite of all-cause mortality, MI, and TVR]. Secondary endpoints included TVR, all-cause mortality, and the composite of all-cause mortality/MI [20]. TVR was defined as a repeat PCI in the same vessel as the index procedure in the presence of ischemic symptoms or positive functional ischemia study on the target vessel area and a significant minimal luminal diameter stenosis of at least 50%. MI was diagnosed by recurrent symptoms, the development of ST-segment elevation or left-bundle branch block on electrocardiography with a CK-MB rise of three times the upper limit of normal and/or positive troponin levels in the laboratory values.

Follow-Up

Clinical status was documented yearly until October 2007 by checking municipal civil registries. A questionnaire, consisting of queries regarding MACE, was sent to all living patients. In case of an event, the hospital medical records of our hospital or the referring institution were systematically reviewed. Most of the repeat interventions were done in our hospital, due to the fact that it is the only tertiary center in the region. The general practitioners or the local cardiologists were called for more information if necessary. The Central Bureau of Statistics (The Hague, The Netherlands) was contacted for the cause of death, if death occurred outside the hospital.

Statistical Analysis

The Student's t test and ANOVA test with post hoc correction were used to compare the unadjusted association between continuous variables and categorical variables, respectively. Cumulative survival curves were generated by the Kaplan–Meier method, and overall incidences were tested with the log-rank test. First, univariate analysis was applied to study the relation between all variables reported in Table I and each end point. All variables that had a P-value $\leq$0.5 in univariable analysis were entered in a separate multivariate Cox regression model for the end points. Backward deletion of the least significant variables was performed until all variables had a P-value of $\leq$0.10.

Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Crude event rates and the adjusted hazard ratios (HR) with a 95% confidence interval (CI) were reported. All statistical tests were two-tailed ($P < 0.05$ regarded as significant) and performed with SPSS for Windows version 15 (SPSS, Chicago, IL).

RESULTS

Sample Characteristics

The follow-up data was complete for 98.4% in the BMS group, 100% in the SES group, and 99.6% in the PES group. Baseline and procedural characteristics of the three groups are shown in Table I. The mean age was 63 years ($\pm$SD 11) and 71% were male. The sum of the follow-up period of the BMS population was 5,345 years compared to 1,483 and 2,943 years for the SES and PES population (Table II).

In summary, patients with a BMS were on average 1 year younger and had more prior revascularization procedures ($P < 0.01$). All the risk factors for coronary artery disease, except smoking, were lower in the BMS group ($P < 0.001$). Complex lesions, longer total stented length, smaller average stent diameter, and more stents per patient were more common in the DES population. Glycoprotein IIb/IIIa inhibitors were more commonly used in the BMS population compared to the SES and PES population ($P < 0.001$). The clopidogrel usage significantly differed between the three groups, being longest in the PES population (6.5 months). The clopidogrel duration and the usage of stents for left main disease or bifurcation lesions

TABLE I. Baseline, Angiographic, and (Peri-)Procedural Characteristics Stratified According to Stent Type

Number of patients	BMS ($n = 1005$)	SES ($n = 373$)	PES ($n = 1071$)	P value
Baseline characteristics				
Demographic characteristics				
Age, years (SD)	62 (11)	61 (10)	63 (11)	<0.01
Male (%)	71.4	70.4	71.1	0.92
Cardiac history (%)				
Prior MI	36.5	32.2	33.0	0.18
Prior CABG	15.1	9.1	11.7	<0.01
Prior PCI	22.6	16.6	17.7	<0.01
Risk factors (%)				
Current smoking	20.3	20.0	16.8	0.10
Hypertension	39.3	48.8	49.8	<0.001
Hypercholesterolemia	54.0	65.6	66.4	<0.001
Diabetes	13.6	18.7	21.0	<0.001
Insulin dependent	1.9	6.9	3.7	<0.001
Noninsulin dependent	11.7	11.7	17.5	<0.001
Family history	22.3	30.7	38.5	<0.001
Angiographic characteristics				
Disease severity				
Multivessel disease (%)	54.3	56.8	55.4	0.70
Bifurcation (%)	3.8	13.1	16.4	<0.001
AHA lesion class (%)				
Type A	23.1	22.9	11.6	<0.001
Type B1	35.8	34.1	29.1	<0.01
Type B2	39.2	49.3	43.5	<0.01
Type C	40.2	41.9	41.6	0.76
(Peri-)procedural characteristics				
Treated vessel (%)				
RCA	41.3	40.5	37.2	0.15
LAD	50.4	59.7	53.0	<0.01
LCX	35.4	38.1	38.7	0.27
LM	3.5	3.5	5.7	<0.05
Bypass graft	5.0	2.1	4.2	0.07
Stent characteristics				
Number of implanted stents (SD)	1.9 (1.3)	2.5 (1.6)	2.5 (1.5)	<0.001
Average stent diameter (mm)	3.2	2.8	2.8	<0.001
Total stented length (mm)	29.7	47.4	50.1	<0.001
Success rate (%)				
Procedural success	93.8	95.5	95.2	0.29
Clinical success	98.2	96.8	98.6	0.07
Platelet aggregration inhibitor				
Clopidogrel duration, months (SD)	2.7 (2.5)	4.7 (3.5)	6.5 (4.0)	<0.001
IIb/IIIa inhibitor (%)	22.7	11.5	12.3	<0.001

increased over time in the three historical cohort groups. Other baseline characteristics were similar.

Clinical Outcome

The cumulative incidence of the primary and secondary end points up to 4 years follow-up is depicted in Fig. 2. The pair-wise comparisons (BMS vs. SES, BMS vs. PES, and SES vs. PES) at 1 and 4 years follow-up are presented in Table II.

At 4 years follow-up, 264 (26.8%) patients receiving a BMS had a MACE, compared to 75 SES patients (20.9%) and 199 PES patients (23.9%) (Fig. 2C).

TABLE II. Crude Event Rates and Multivariate Analysis Stratified According to Different Stent Types

	Number of events (%)			Multivariatea HRb [95% CIc]		
	BMS (n = 1005)	SES (n = 373)	PES (n = 1071)	BMS versus SES	BMS versus PES	SES versus PES
TVR						
1 year	115 (11.6%)	27 (7.1%)	67 (6.0%)	0.44 [0.28–0.69]	0.65 [0.55–0.76]	0.86 [0.55–1.34]
4 years	170 (17.8%)	45 (12.5%)	107 (11.8%)	0.53 [0.37–0.75]	0.71 [0.62–0.81]	0.89 [0.62–1.26]
Δ1–4 years	55 (6.2%)	18 (5.4%)	40 (5.8%)	0.71 [0.41–1.24]	0.85 [0.68–1.06]	0.93 [0.53–1.65]
MACE						
1 year	152 (13.6%)	37 (10.0%)	115 (9.6%)	0.50 [0.34–0.73]	0.55 [0.42–0.72]	1.02 [0.70–1.48]
4 years	264 (26.8%)	75 (20.9%)	199 (23.9%)	0.62 [0.47–0.81]	0.67 [0.55–0.82]	1.09 [0.83–1.43]
Δ1–4 years	112 (13.2%)	38 (10.9%)	84 (14.3%)	0.80 [0.55–1.19]	0.94 [0.81–1.10]	1.20 [0.80–1.79]
Mortality/MI						
1 year	47 (4.8%)	15 (3.5%)	60 (5.7%)	0.87 [0.48–1.58]	1.20 [0.81–1.77]	1.26 [0.71–2.24]
4 years	118 (12.1%)	39 (11.0%)	110 (12.7%)	0.95 [0.65–1.37]	1.12 [0.86–1.48]	1.20 [0.82–1.75]
Δ1–4 years	71 (7.3%)	24 (7.5%)	50 (7%)	1.00 [0.63–1.62]	1.02 [0.84–1.24]	1.14 [0.68–1.90]
Mortality						
1 year	32 (3.3%)	6 (1.6%)	37 (3.5%)	0.53 [0.22–1.28]	1.11 [0.68–1.80]	1.75 [0.73–4.19]
4 years	95 (9.5%)	28 (8.0%)	82 (9.7%)	0.87 [0.57–1.34]	1.09 [0.80–1.50]	1.33 [0.85–2.08]
Δ1–4 years	63 (6.2%)	22 (6.4%)	45 (6.2%)	1.06 [0.64–1.74]	1.03 [0.84–1.26]	0.95 [0.57–1.60]
Sum follow-up (years)	5344.6	1483.2	2942.7			

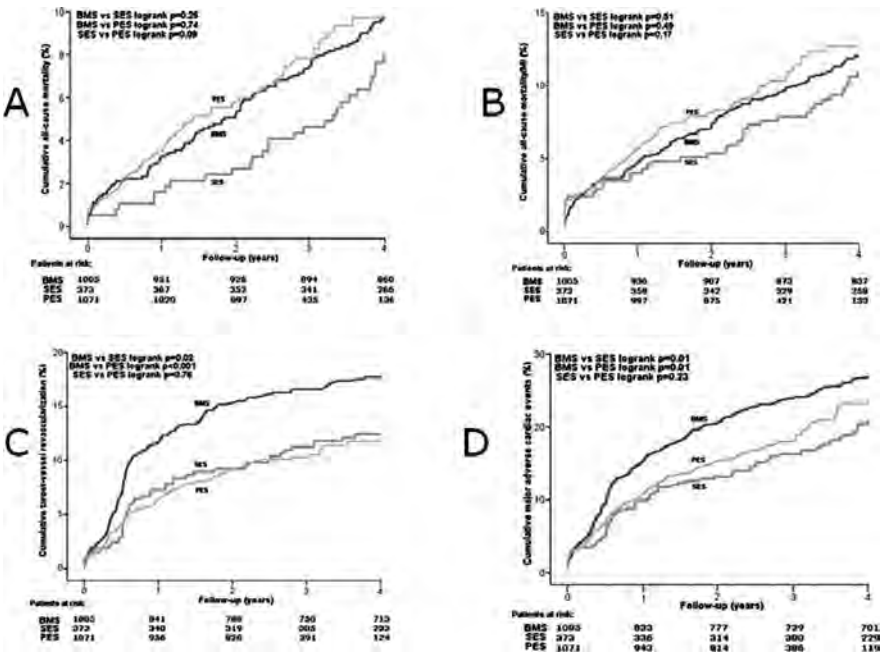

Fig. 2. Adverse events in patients treated with BMS, SES, and PES: (A) cumulative all-cause mortality curve; (B) all-cause mortality/MI curve; (C) TVR curve; and (D) MACE curve.

TABLE III. Cumulative Incidence of Definite Stent Thrombosis According to Stent Type Implanted Between January 2000 and December 2005

	BMS [*n* (%)]	SES [*n* (%)]	PES [*n* (%)]	*P* value
Early	3 (0.3)	3 (0.8)	8 (0.7)	0.3
Acute	2 (0.2)	1 (0.3)	4 (0.4)	0.8
Subacute	1 (0.1)	2 (0.5)	4 (0.4)	0.3
Late	2 (0.2)	1 (0.3)	2 (0.2)	0.9
Very late	3 (0.3)	1 (0.3)	7 (0.7)	0.4
Total	8 (0.8)	5 (1.3)	17 (1.6)	0.5

Unadjusted, patients with a SES or PES had less MACE compared to BMS patients (HR = 0.72, 95% CI (95% CI): 0.56–0.94; HR = 0.89, 95% CI: 0.81–0.98, respectively). The occurrence of MACE was significantly lower in the SES and PES patients compared to BMS patients, mainly due to less TVR procedures (HR = 0.67, 95% CI: 0.48–0.93; HR = 0.79, 95% CI: 0.70–0.89, respectively) (Fig. 2C). The cumulative incidence of all-cause mortality (BMS = 9.5%; SES = 8.0%; and PES 9.7%) and the composite endpoint of all-cause mortality/MI (BMS = 12.1%; SES = 11.0%; and PES = 12.7%) was similar between BMS, SES, and PES (Fig. 2A and B). The occurrence of early, late, and very late stent thrombosis was equally rare in the three groups (Table III).

The independent predictors of TVR were prior PCI (HR = 1.30, 95% CI: 1.00–1.70), prior coronary artery bypass graft (HR = 1.70, 95% CI: 1.27–2.29), hypercholesterolemia (HR = 1.36, 95% CI: 1.07–1.73), treatment of the left-anterior descending coronary artery (HR = 1.33, 95% CI: 1.05–1.68), and total stented length (HR = 1.01, 95% CI: 1.01–1.01).

After separately adjusting for the potential confounders of the different end points, all-cause mortality and the composite end point all-cause mortality/MI remained nonsignificant between the three groups (Table II). Mainly due to the fact that SES and PES were superior to BMS with respect to TVR after 1 year (HR = 0.44, 95% CI: 0.28–0.69; HR = 0.65, 95% CI: 0.55–0.76, respectively) and 4 years (HR = 0.53, 95% CI: 0.37–0.75; HR = 0.71, 95% CI: 0.62–0.81, respectively), the occurrence of MACE was significantly lower (HR = 0.62, 95% CI: 0.47–0.0.81; HR = 0.67, 95% CI: 0.55–0.82, respectively) (Table II). The benefit on TVR and MACE rates in the SES- and PES-group compared to the BMS-group was caused by less events first-year post-PCI (Table II). The HRs for the events occurring between 1 and 4 years were similar between the three groups. No significant differences were found between SES and PES for TVR procedures and MACE at each year of follow-up.

DISCUSSION

This study reports the 4-year follow-up of BMS, SES, and PES in real-world patient cohorts for the percutaneous treatment of stable CAD. The main finding of the study is that SES and PES reduced TVR procedures with an average of 50% when compared with BMS implantation, whereas MACE rates decreased by 34% compared to BMS at 4-year follow-up. The all-cause mortality rates and the composite end point all-cause mortality/MI rates were similar between the three groups. Also, no significant differences were found between SES and PES for all end points. Although the TVR procedures were only performed if clinically driven, some patients with complex lesions in the SES population had an angiographic follow-up at 6-months in which angiographically driven TVR might have occurred. This offers an explanation for the sudden rise in TVR rates at 6 months. The convergence of the all-cause mortality graphic for the SES population toward the BMS population and PES population at 4 years follow-up is intriguing. This trend could not be attributed to more occurrence of very late stent thrombosis in the SES population but might be caused due to reasons unrelated to stent implantation, such as baseline differences in the populations.

The findings of this study are different from a registry (n = 874) that reported on the use of DES and BMS for stable coronary artery disease [15]. Horst et al. [15] showed that although DES decreased the MACE rates in the first 12 months post-PCI compared to BMS (HR = 0.51, 95% CI: 0.36–0.71), the effect was not sustained until the third year of follow-up due to increased event rates after 12 months in the DES group (HR = 1.36, 95% CI: 0.94–1.96). However, the real outcome could be masked due to early clopidogrel cessation by the majority of DES patients despite the ACC/AHA recommendations, resulting in a rebound effect [21,22]. Despite the guidelines recommend 12 months of clopidogrel use post-DES implantation, only 38% of the patients in the DES-group was still using clopidogrel. This difference in short- and long-term HR rates was not found in this study, in which the early advantage in terms of TVR due to inhibition of neointimal hyperplasia was sustained after the first year. The lack of catch up on TVR rates in the DES populations, but also the lack of cumulative advantage on the long-term, indicates that there is no continuing additional advantage beyond the first year.

Although the findings of our study differed from a prior study comparing DES with BMS, it corresponded well with our expectations, because DESs have a plausible manner for blocking the restenotic cascade that occur after coronary stent implantation. Sirolimus

inhibits the cell cycle from the G1 to S phase by acting on the mammalian target of rapamycin after binding to the FKBP12 protein. Paclitaxel has the ability to stabilize microtubules causing a blockage in the G0/G1 and G2/M cell-cycle phases. The blockage of these processes after implanting a DES in the coronary artery, such as the inflammatory response and the neointimal hyperplasia, results in less lumen loss compared to BMS.

The safety and efficacy of the SES and the PES have been demonstrated in the landmark RAVEL trial ($n = 238$), SIRIUS trial ($n = 1058$), and TAXUS family trials ($n = 536$) [11,12,23]. An impressive reduction in TVR procedures and MACE rates with the use of SES or PES was shown in these trials, which were completely in line with our findings. Randomized trials comparing PES with SES found different results in the past, making it hard to determine whether PES or SES outperformed the other [24–29]. A recent meta-analysis ($n = 3669$) showed that SES decreased restenosis rates (OR = 0.68; 95% CI: 0.55–0.86) and TVR procedures (OR = 0.64; 95% CI: 0.49–0.84) compared to PES [30]. Also, the occurrence of stent thrombosis was higher in the PES population (HR = 0.66, 95% CI: 0.46–0.94), although this did not lead to a higher risk for death compared to the SES population [31].

Despite the superiority of DES compared the BMS for the percutaneous treatment of stable angina, the current guidelines recommend optimal medical treatment as the initial strategy for stable angina and not coronary angioplasty [32,33]. These guidelines were also endorsed in a meta-analysis ($n = 2950$) that showed no differences on clinical end points [34]. In contrast to these findings and the current guidelines, a more recent and larger meta-analysis ($n = 7513$) consisting of 17 randomized controlled trials showed that patients with stable coronary artery disease were better off with a PCI than optimal medical treatment for the occurrence of all-cause mortality (OR = 0.80, 95% CI: 0.64–0.99) [4]. However, this meta-analysis had some shortcomings. First, the included trials did not research the two treatment arms head-to-head, because all the patients received optimal treatment regardless in which treatment arm they were included. Second, both treatment arms substantially changed in the 17-year enrollment period. Third, some patients included in the optimal medical treatment arm actually did receive a revascularization procedure during the follow-up period, eventually obscuring the true results of both arms.

The results of this study must be interpreted with caution due to some limitations. First of all, it is a single-center, nonrandomized, observational cohort study. Therefore, leading to unidentical groups, in which the complexity of the procedures performed increased substantially, mainly caused by the long inclusion period of 5 years. Although multivariate analysis was done to adjust for these baseline differences, it remains uncertain whether this was sufficient to fully correct for the dissimilarities. Even so, the risk profile of patients receiving a DES was greater than the BMS patients. Nevertheless, the possibility that a randomized trial between DES and BMS will be conducted for the percutaneous treatment of stable coronary artery disease is at this stage unethical. Second, due to continuous enrollment of patients from January 2000 until December 2005, some did not complete the 4 years follow-up. Therefore, especially the 95% CI should be taken into account when interpreting the results. Finally, the data was not collected by direct contact with the included patients but rather relied on the patient's ability to remember events. Some events could have been forgotten by the patients.

In conclusion, using SES and PES have significant benefits compared to BMS, in terms of decreased need for TVR procedures and the occurrence of MACE. The early advantage in TVR earned by SES and PES over BMS is sustained at 4 years of follow-up. No difference was found for all-cause mortality or for the composite endpoint all-cause mortality/MI. The outcome of SES and PES was similar for all end points. The implantation of SES or PES should be the preferred choice in the percutaneous treatment of stable angina.

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APPENDIX

The following operators were involved in the procedures of the discussed patient populations: Chourmouzios A. Arampatzis, MD, Eugene McFadden, MD, PhD, Pim J. de Feyter, MD, PhD, Willem J. van der Giessen, MD, PhD, Sjoerd H. Hofma, MD, PhD, Angela Hoye, MBChB, MRCP, Peter P.T. de Jaegere, MD, PhD, Patrick W. Serruys, MD, PhD, Evelyn Regar, MD, PhD, Georgios Sianos, MD, PhD, and Pieter C. Smits, MD, PhD.

Part III

PERCUTANEOUS REVASCULARIZATION IN 'ALL COMERS'; THE IMPORTANCE OF STENT TYPE

3.1

The Unrestricted Use of Sirolimus- and Paclitaxel-Eluting Stents Results in Better Clinical Outcomes During 6-Years Follow-up than Bare-Metal Stents. An analysis from the RESEARCH and T-SEACRH registries.

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The Unrestricted Use of Sirolimus- and Paclitaxel-Eluting Stents Results in Better Clinical Outcomes During 6-Year Follow-Up Than Bare-Metal Stents

An Analysis of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and T-SEARCH (Taxus–Stent Evaluated At Rotterdam Cardiology Hospital) Registries

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Objectives The aim of this study was to assess the 6-year clinical outcome after unrestricted use of sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) as compared with bare-metal stents (BMS) in consecutive de novo patients undergoing percutaneous coronary intervention (PCI).

Background SES and PES have been shown to significantly decrease target vessel revascularization (TVR) rates compared with BMS in "real-world" registries. However, possible higher rates of very-late stent thrombosis and a restenosis "catch-up" trend might jeopardize the benefit.

Methods Three PCI cohorts, each with exclusive use of 1 stent type (BMS = 450; SES = 508; PES = 576), were systematically followed for the occurrence of major adverse cardiac events (MACE).

Results Very-late stent thrombosis was more common in SES and PES patients than BMS patients (2.4% vs. 0.9% vs. 0.4%, respectively; p = 0.02); however, there were no significant differences between the stent types for all-cause mortality and all-cause mortality/myocardial infarction at 6-year follow-up. Sixty-nine SES patients (Kaplan-Meier estimate 14%) and 72 PES patients (14%) had a TVR, as compared with 79 BMS patients (18%; log-rank p = 0.02), which maintained significance after adjustment for (potential) confounders. Multivariate analysis showed that DES implantation is associated with lower incidence of TVR and MACE than BMS implantation (hazard ratio: 0.65, 95% confidence interval: 0.49 to 0.86; p = 0.003; hazard ratio: 0.79, 95% confidence interval: 0.65 to 0.97; p = 0.02, respectively). Incidence of MACE was also lower in SES and PES patients (30% and 30%, respectively) than in BMS patients (34%); however, significance was borderline.

Conclusions The unrestricted use of both DES resulted in a sustained advantage in decreasing TVR and, to a lesser extent, MACE compared with BMS at 6 years. The SES and PES are equally safe and effective in the treatment of coronary lesions. (J Am Coll Cardiol Intv 2010;3:1051–8)

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In the last decade several randomized clinical trials and registries assessed the short- and long-term clinical outcome of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) (1–6). Although drug-eluting stents (DES) lead to a decrease in angiographic restenosis and target vessel revascularization (TVR) rates compared with bare-metal stents (BMS), DES caused novel safety concerns such as possible higher very-late stent thrombosis rates (7,8). The occurrence of stent thrombosis is not merely a result of premature discontinuation of dual antiplatelet therapy but rather a multifactorial problem caused by several detrimental features, including clinical, coronary lesion, and procedural characteristics (9–14). The higher likelihood of late stent malapposition after DES implantation, which is associated with very-late stent thrombosis (≥1 year after stent implantation), could jeopardize the very long-term clinical beneficial value of DES. Also the observation of a possible clinical TVR "catch-up" phenomenon in the DES-population is of concern (15–18).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TVR = target vessel revascularization

The long-term clinical results of the treatment of "all-comer" percutaneous coronary intervention (PCI) patients without using any exclusion criteria have been described by our group in the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus–Stent Evaluated At Rotterdam Cardiology Hospital) registries (19,20). Although DES have shown superior short- and long-term clinical outcome with regard to TVR rates compared with BMS, it remains unknown whether this effect is sustained. Therefore, the purpose of the present report is to investigate the safety and efficacy profile of the unrestricted use of SES and PES versus BMS in de novo patients undergoing PCI at 6-year follow-up.

Methods

Patient population and study design. During specific time periods between October 2001 and September 2003, a total of 1,534 consecutive de novo patients were treated with PCI in 3 "real world" registries (Fig. 1). All patients remained in their first original enrolled cohort during the follow-up period, and those receiving multiple stent types during the initial procedure were excluded from analysis. In total, 508 consecutive patients underwent a PCI from April 2002 until October 2002 in which only SES (Cypher, Cordis Corp., Johnson & Johnson, Warren, New Jersey) were implanted as part of the RESEARCH registry (19). From February 2003 until September 2003, 576 "all-comer" patients were treated with the PES (TAXUS, Express2, or Liberté; Boston Scientific, Natick, Massachusetts) as the default strategy for all PCI as part of the T-SEARCH registry (20). These patients were compared with 450 BMS patients treated in the last 6-month period of the pre-SES era.

The RESEARCH and T-SEARCH registries have been described previously and were conducted according to the dynamic registry design described by Rothman et al. (21). All procedures were performed according to standard clinical guidelines, and every patient was pre-treated with aspirin and ≥300 mg of clopidogrel. The post-PCI antiplatelet regimen consisted of ≥80 mg aspirin lifelong and ≥75 mg clopidogrel for at least 1 month if BMS were used, ≥3 months for patients with SES, and ≥6 months for patients with PES. Periprocedural glycoprotein IIb/IIIa antagonists were used at the discretion of the treating interventional cardiologist. All of the repeat coronary angiographies were clinically driven for the BMS group. Due to specific subgroup analysis 18% of the PES patients and 36% of the SES patients had a scheduled repeat coronary angiography at 6 months, in which nonclinically driven TVR might have occurred. After 6 months, all coronary angiographies of the SES and PES patients were clinically driven by physical symptoms or diagnostic findings suggestive of myocardial ischemia. The study protocol was approved by the institutional ethics committee, and all patients provided written informed consent.

Definitions and clinical end points. Procedural success was defined as successful stent deployment and a residual stenosis <30% by visual analysis in the presence of Thrombolysis in Myocardial Infarction flow grade 3 without the occurrence of MACE within 2 days after intervention.

Definite stent thrombosis was defined as angiographically documented thrombus in or within 5 mm of the stent, accompanied by at least 1 of the following (as recommended by the Academic Research Consortium criteria): 1) acute symptoms; 2) ischemic electrocardiographic changes; and 3) typical rise and fall of cardiac markers. Stent thrombosis was categorized into early (within 30 days after stent implantation), late (within 30 days and 1 year after stent implantation), and very-late (after 1 year after stent implantation).

The primary end point was the occurrence of patient-orientated MACE (defined as a composite of all-cause mortality, any myocardial infarction [MI], and TVR). Efficacy end point included TVR, whereas safety end points consisted of stent thrombosis, all-cause mortality, and the composite of all-cause mortality/any MI. Myocardial infarction was diagnosed by recurrent typical clinical symptoms, the development of ST-segment elevation or left bundle branch block on electrocardiography with a creatine kinase-myocardial band rise of 3× the upper limit of normal and/or

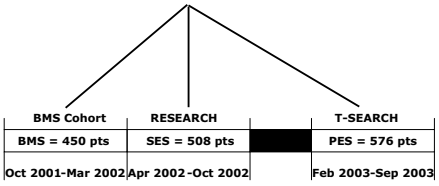

Figure 1. Chronological Order of the 3 Cohorts (n = 1,534)

The 3 cohorts (bare-metal stent [BMS] cohort/RESEARCH [Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital] and T-SEARCH [Taxus–Stent Evaluated At Rotterdam Cardiology Hospital] registries). The combined use of different types of stents in the same procedure resulted in exclusion of the patient. If patients had multiple revascularization procedures, they were only enrolled in the first original cohort. PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

positive troponin levels in the laboratory values. A TVR was defined as a repeat PCI in the same vessel as the index procedure, in the presence of ischemic symptoms, or positive functional ischemia study on the target vessel area and a significant minimal luminal diameter stenosis of at least 50%.

Follow-up. The municipal civil registries were contacted yearly until December 2009 to document the clinical status of treated patients. All living patients received a questionnaire, consisting of queries regarding repeat hospital stay and MACE. In case of a suspected event, the medical records and coronary angiographies from our hospital or the referring institution were systematically reviewed by 2 independent experienced interventional cardiologists.

Statistical analysis. Continuous baseline variables were tested with the analysis of variance test with post-hoc correction, and the chi-square test was used for the categorical baseline variables. The estimated cumulative adverse cardiac events for the end points (MACE, TVR, mortality, and mortality/MI) were generated with the Kaplan-Meier method, and the differences among the 3 stent curves were tested with the log-rank test.

A multivariate Cox proportional hazard regression model (95% confidence interval [CI] and p value <0.05 regarded as significant) including all variables that had a p value ≤ 0.5 in univariable analysis was used to adjust for baseline characteristics. Backward deletion of the least significant variables was performed until all variables had a p value of $\leq$ 0.10 (these variables included age, hypercholesterolemia, prior intervention, diabetes, multivessel disease, left main disease, bypass graft stenting, type b2 lesion, number of stents implanted, and total stented length). Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All statistical analyses were performed with SPSS for Windows version 15 (SPSS, Inc., Chicago, Illinois).

Results

Population characteristics. Survival status was available for 98% of the patients. The baseline and procedural characteristics of the BMS, SES, and PES groups are shown in Table 1. In summary, the population consisted mostly of men (71%), and the mean age was 61 years ($\pm$ 11.1 years). There were no significant differences in baseline characteristics among the 3 groups, except for BMS patients who had more prior PCIs ($p < 0.01$) compared with SES and PES patients. Significantly more patients presented with an acute coronary syndrome in the PES group. Type C and bifurcation lesions were more often treated in the SES and PES groups ($p < 0.01$). There were more stents with smaller diameters implanted in the SES and PES patients with a longer total stented length compared with BMS patients ($p < 0.01$).

The usage of glycoprotein IIb/IIIa inhibitors was more common in the BMS population compared with the SES and PES population ($p < 0.01$). The duration of clopidogrel usage after stent implantation increased over time, being shortest for the BMS group (mean of 1 month) and longest in the PES population (mean of 6 months).

6-year outcome: safety end points. The cumulative incidence and the associated adjusted multivariate hazard ratios (HRs) (BMS vs. SES, BMS vs. PES, SES vs. PES) of the 6-year follow-up of the BMS, SES, and PES cohorts are shown in Table 2 for each of the safety end points (i.e., stent thrombosis, all-cause mortality, and all-cause mortality/any MI).

Although very-late stent thrombosis was more common in SES patients than BMS patients (SES = 2.4% vs. PES = 0.9% vs. BMS = 0.4%; [analysis of variance] p value = 0.02; [Bonferroni-test] BMS vs. SES = 0.02, BMS vs. PES = NS, SES vs. PES = NS), it did not influence the incidence of the end points all-cause mortality and the composite end point of all-cause mortality or MI at 6-year follow-up on multivariate analysis (Tables 2 and 3).

6-year outcome: efficacy end points. Univariate analysis showed that there were no significant differences in MACE and TVR rates between SES and PES at 6 years (HR: 0.95, 95% CI: 0.85 to 1.06; HR: 1.02, 95% CI: 0.87 to 1.21, respectively) and therefore we could analyze both SES and PES together as a broader DES group (n = 1,084). The TVR rates of PES patients were significantly lower compared with BMS patients (HR: 0.84, 95% CI: 0.71 to 0.98) and borderline significant for SES patients (HR: 0.86, 95% CI: 0.73 to 1.01). DES significantly reduced TVR rates (HR: 0.72, 95% CI: 0.55 to 0.95); however, MACE rates were similar (HR: 0.91, 95% CI: 0.75 to 1.10).

Table 1. Baseline and Procedural Characteristics Stratified According to Stent Type

	BMS (n = 450)	SES (n = 508)	PES (n = 576)	p Value
Demographic characteristics				
Age, yrs (±SD)	60.8 (±10.9)	61.1 (±11.0)	61.7 (±11.4)	0.3
Male (%)	70.4	67.9	73.6	0.4
Cardiac history				
Prior MI	39.7	29.9	34.5	<0.01
Prior CABG	8.0	9.3	6.1	0.4
Prior PCI	18.0	18.7	18.2	0.8
Risk factors				
Current smoking	34.0	30.7	29.0	0.3
Hypertension	37.6	41.3	41.8	0.2
Hypercholesterolemia	55.3	55.5	62.2	1.0
Diabetes	14.9	17.7	18.4	0.3
Insulin-dependent	4.0	5.9	5.2	0.2
Non–insulin-dependent	10.9	11.8	13.4	0.7
Family history	28.2	32.5	40.6	0.2
Clinical presentation				
Stable angina	47.3	44.3	44.8	0.6
Unstable angina	34.7	37.2	27.1	<0.01
Acute myocardial infarction	17.8	18.1	28.1	<0.01
Cardiogenic shock	2.0	1.8	3.6	0.1
Disease severity				
Multivessel disease	47.8	54.1	56.1	0.1
Bifurcation	7.8	15.7	16.0	<0.01
Number of stents (±SD)	1.8 (±1.1)	2.2 (±1.4)	2.2 (±1.5)	<0.01
Average stent diameter, mm	3.2	2.8	3.0	<0.01
Total stent length, mm	30.1	38.8	42.9	<0.01
Treated vessel				
RCA	34.0	38.6	37.8	0.1
LAD	59.3	58.7	55.4	0.9
LCX	32.9	31.7	33.3	0.7
LM	2.2	3.0	4.3	0.6
Bypass graft	2.0	3.3	3.3	0.2
AHA lesion class				
Type A	19.6	21.9	7.3	0.2
Type B1	31.8	30.7	25.0	0.8
Type B2	49.3	48.6	54.3	0.8
Type C	29.8	42.5	47.2	<0.01
Success rate				
Procedural success	97.3	97.2	97.4	0.9
Thrombocyte aggregation inhibitor				
Clopidogrel duration, months (±SD)	1.0 (±0.1)	4.2 (±2.0)	6 (±0.0)	<0.01
Glycoprotein IIb/IIIa inhibitor	33.3	19.3	27.6	<0.01

Data are presented as percentages or mean (±SD), unless otherwise indicated.

AHA = American Heart Association; BMS = bare-metal stent(s); CABG = coronary artery bypass graft; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); RCA = right coronary artery; SES = sirolimus-eluting stent(s).

The multivariate Cox regression analysis showed that MACE rates were lower in the DES group compared with the BMS group (HR: 0.79, 95% CI: 0.65 to 0.97). This was primarily because significantly fewer TVR procedures were performed in the DES group (HR: 0.65, 95% CI: 0.49 to 0.86). The same findings were present for TVR when SES and PES were independently compared with BMS (HR: 0.81, 95% CI: 0.68 to 0.96; and HR: 0.81, 95% CI: 0.68 to 0.96, respectively) with lower Kaplan-Meier estimates (14% and 18%; log-rank p = 0.02, respectively) (Figs. 2 and 3),

Table 2. Crude Event Rates and Multivariate Analysis Stratified According to Different Stent Types at 6 Years

	n (%)			Multivariate HR (95% CI)		
	BMS (n = 450)	SES (n = 508)	PES (n = 576)	BMS vs. SES	BMS vs. PES	PES vs. SES
Mortality						
2-yr	28 (6.2%)	29 (5.7%)	43 (7.5%)	0.90 (0.69–1.18)	0.97 (0.75–1.26)	0.96 (0.75–1.23)
6-yr	77 (17.1%)	83 (16.3%)	92 (16.0%)	1.00 (0.85–1.18)	0.97 (0.82–1.15)	1.00 (0.86–1.17)
Δ2–6 yrs	49 (10.9%)	54 (10.6%)	49 (8.5%)	0.95 (0.84–1.09)	0.86 (0.56–1.33)	0.98 (0.80–1.12)
Mortality/MI						
2-yr	53 (11.8%)	49 (9.6%)	67 (11.6%)	0.88 (0.72–1.08)	0.97 (0.79–1.18)	0.98 (0.81–1.18)
6-yr	105 (23.3%)	111 (21.9%)	122 (21.2%)	0.97 (0.84–1.11)	0.94 (0.81–1.08)	1.02 (0.89–1.17)
Δ2–6 yrs	52 (11.5%)	62 (12.3%)	55 (9.6%)	0.94 (0.83–1.06)	0.92 (0.60–1.40)	0.92 (0.76–1.12)
TVR						
2-yr	63 (14.0%)	39 (7.7%)	52 (9.0%)	0.66 (0.54–0.82)	0.77 (0.63–0.93)	0.95 (0.77–1.18)
6-yr	79 (17.6%)	69 (13.6%)	72 (12.5%)	0.81 (0.68–0.96)	0.81 (0.68–0.96)	1.06 (0.89–1.26)
Δ2–6 yrs	16 (3.6%)	30 (5.9%)	20 (3.5%)	0.87 (0.71–1.07)	0.83 (0.42–1.64)	0.86 (0.64–1.15)
MACE						
2-yr	99 (22.0%)	77 (15.2%)	106 (18.4%)	0.75 (0.64–0.88)	0.85 (0.74–0.99)	0.96 (0.82–1.11)
6-yr	153 (34.0%)	151 (29.7%)	172 (29.9%)	0.90 (0.80–1.01)	0.89 (0.79–1.00)	1.01 (0.90–1.14)
Δ2–6 yrs	54 (12.0%)	74 (14.5%)	66 (11.5%)	0.92 (0.82–1.04)	0.80 (0.54–1.18)	0.96 (0.80–1.14)

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; other abbreviations as in Table 1.

although significance was borderline for MACE (HR: 0.90, 95% CI: 0.80 to 1.01; and HR: 0.89, 95% CI: 0.79 to 1.00, respectively). No significant differences were observed for MACE and TVR rates between SES and PES.

Discussion

The 2-year follow-up of the T-SEARCH registry and the 4-year follow-up of the RESEARCH registry have already been published (3,22). Briefly, there were no significant differences in MACE between PES and SES (18.9% vs. 15.4%, p = 0.12) in the T-SEARCH registry at 2-year follow-up, but the incidence of MACE was higher in the BMS group compared with the SES group (28.7% vs. 23.0%, p = 0.05) in the RESEARCH registry at 4-year follow-up. The main finding of the 6-year follow-up of the RESEARCH and T-SEARCH registries is that DES reduced TVR by 35% and MACE by nearly 20% compared with BMS at 6-year follow-up in an unselected population. Although several clinical trials found contradictory results for SES outperforming PES in terms of TVR rates, no significant differences were found between SES and PES for all investigated end points at 6 years in our study (23–28). The Kaplan-Meier curve illustrates that the TVR- and MACE-graphic lines for both DES remain nearly parallel to the BMS-graphic line after 1 year of follow-up, proving

Table 3. Incidence of ST in the 3 PCI Cohorts

	n (%)				
	BMS (n = 450)	SES (n = 508)	PES (n = 576)	ANOVA p Value	Bonferroni Test
Early ST	8 (1.8%)	2 (0.4%)	7 (1.2%)	0.1	NS
Acute ST	4 (0.9%)	1 (0.2%)	1 (0.2%)	0.3	NS
Subacute ST	4 (0.9%)	1 (0.2%)	6 (1%)	0.2	NS
Late ST	2 (0.4%)	2 (0.4%)	4 (0.7%)	0.8	NS
Very-late ST	2 (0.4%)	12 (2.4%)	5 (0.9%)	0.02	BMS vs. SES = 0.02 BMS vs. PES = NS SES vs. PES = NS
Total ST	12 (2.7%)	16 (3.1%)	16 (2.8%)	0.9	NS

Stent thrombosis (ST) occurring within 30 days after stent implantation is defined as early ST, categorized into acute ST (within 24 h) and subacute ST (1 to 30 days). Late ST is defined as ST occurring between 30 days and 1 year. Stent thrombosis occurring >1 year after the index procedure is defined as very-late ST.

ANOVA = analysis of variance; other abbreviations as in Tables 1 and 2.

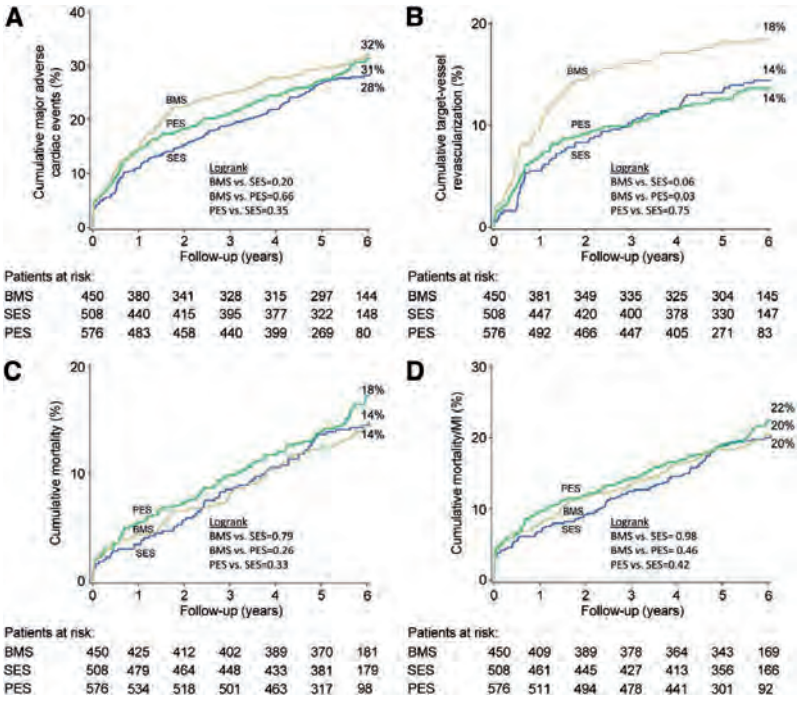

Figure 2. Kaplan-Meier Curves According to Stent Type for the End Points

Adverse cardiac events with the associated log-rank test of patients treated with BMS, SES, and PES: **(A)** major adverse cardiac event curve; **(B)** target vessel revascularization curve; **(C)** mortality curve; and **(D)** mortality/myocardial infarction (MI) curve. Abbreviations as in Figure 1.

that the beneficial effect in reducing neointimal hyperplasia occurs in the first year, but most importantly the effect is sustained at 6 years.

The 5-year results of the RAVEL (RAndomized study with the sirolimus-eluting VELocity balloon-expandable stent4) clinical trial, which compared the SES with the BMS in patients with single de novo coronary lesions, showed that target-lesion revascularization and MACE rates were lower in SES patients compared with BMS patients (10.3% vs. 26%, $p < 0.001$; 25.8% vs. 35.2%, $p = 0.03$, respectively) (3). These results were reproduced in the 5-year clinical outcome results of the SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial (SES = 9.4% vs. BMS = 24.4%, $p < 0.001$; SES = 20.3% vs. BMS = 33.5%, $p < 0.001$, respectively) and the TAXUS (TAXUS IV-SR: Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent) trial (PES = 16.9% vs. BMS = 27.4%, $p < 0.001$; PES = 24.0% vs. BMS = 32.8%, $p < 0.001$) (5,29). The findings of these clinical trials are mostly in line with the results found in our registries, in which we have used patient-orientated MACE (death, any MI, any revascularization) instead of device-orientated MACE (cardiac death, target-vessel related MI, and target-lesion revascularization).

Although there were more patients with very-late stent thrombosis in the SES and PES groups, it did not influence the safety outcome of either stent. In spite of controversial findings of several large (multicenter) registries and clinical trials concerning the possibility of an increased risk of definite very-late stent thrombosis with SES and PES implantation compared with BMS implantation, DES implantation has never been associated with higher mortality rates (30–32). Even though some factors causing very-late stent thrombosis are patient (behavior)-related, the higher

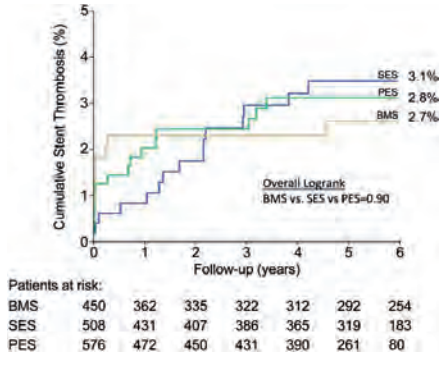

Figure 3. Kaplan-Meier Curves According to Stent Type for Stent Thrombosis

Abbreviations as in Figures 1 and 2.

occurrence of late stent malapposition in SES and PES patients compared with BMS is a stent type-related factor contributing to higher stent thrombosis rates (33). Previously published larger studies showed higher late stent thrombosis rates in the PES population than in the SES population (34,35). However, the main factor causing this difference in stent thrombosis rates between the different stents remains undetermined, because of considerable differences in stent design (closed-cell design of the SES, and the different strut thicknesses of the first- [132 μm] and second-generation [97 μm] PES), dissimilar stent rigidity, and inability to compare anti-restenotic mechanisms of the drug and drug-release patterns of the stent platforms used (36,37).

Although "real-world" registries are the best way to mimic the complex clinical situation of most patients, several shortcomings need to be addressed and acknowledged. Because the described cohorts are single-center, nonrandomized, and purely observational, they have different complexity levels. During the inclusion years, increasingly more diseased patients and more complex lesions were being treated with PCI. Although this has been corrected for in statistical analysis, it is debatable whether this was sufficient. Because the BMS population consisted of the least complex patients and it had higher TVR rates and MACE rates than SES and PES, the BMS has proven to be inferior. It is noteworthy that nearly 20% of the SES patients and 40% of the PES patients had a planned angiographic follow-up at 6 months. This is a possible explanation for the sudden rise of TVR rates at 6-month follow-up in the DES groups, in which oculostenotic-driven TVR might have occurred that had a negative influence on the end point, which actually strengthens our current findings showing that DES have a better clinical safety and efficacy compared with BMS. Third, some cardiac events could have been missed, because of data collection relied on the ability of the patient to remember events of the past year. However, we have no reason to believe that this was not identically distributed between the stent cohorts. Finally, the sample size of this study led to inadequate statistical power for detecting differences for stent thrombosis in the 3 cohorts.

The 6-year follow-up of the RESEARCH and T-SEARCH registries shows that SES and PES have a beneficial effect on safety and efficacy outcome compared with BMS, in terms of decreased TVR procedures and, to a lesser extent, MACE when used in unselected de novo patients. Although the occurrence of more very late stent thrombosis in SES and PES patients remains a safety concern, this did not influence the safety end points all-cause mortality and the composite end point all-cause mortality/MI, which were equally distributed. The safety and efficacy outcomes for SES and PES were similar for all end points.

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Key Words: bare-metal stent(s) ■ paclitaxel-eluting stent(s) ■ sirolimus-eluting stent(s) ■ target vessel revascularization.

3.2

Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study.

Magro M, Raber L, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, Wenaweser P, Daemen J, Meier B, Jüni P, Serruys PW, Windecker S.

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Very Late Coronary Stent Thrombosis of a Newer-Generation Everolimus-Eluting Stent Compared With Early-Generation Drug-Eluting Stents

A Prospective Cohort Study

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Background—Early-generation drug-eluting stents releasing sirolimus (SES) or paclitaxel (PES) are associated with increased risk of very late stent thrombosis occurring >1 year after stent implantation. It is unknown whether the risk of very late stent thrombosis persists with newer-generation everolimus-eluting stents (EES).

Methods and Results—We assessed the risk of stent thrombosis in a cohort of 12 339 patients with unrestricted use of drug-eluting stents (3819 SES, 4308 PES, 4212 EES). Results are incidence rates per 100 person-years after inverse probability of treatment weighting to adjust for group differences. During follow-up of up to 4 years, the overall incidence rate of definite stent thrombosis was lower with EES (1.4 per 100 person-years) compared with SES (2.9; hazard ratio, 0.41; 95% confidence interval, 0.27–0.62; $P<0.0001$) and PES (4.4; hazard ratio, 0.33; 95% confidence interval, 0.23–0.48; $P<0.0001$). The incidence rate per 100 person-years of early (0–30 days), late (31 days–1 year), and very late stent thrombosis amounted to 0.6, 0.1, and 0.6 among EES-treated patients; 1.0, 0.3, and 1.6 among SES-treated patients; and 1.3, 0.7, and 2.4 among PES-treated patients. Differences in favor of EES were most pronounced beyond 1 year, with a hazard ratio of 0.33 (EES versus SES; $P=0.006$) and 0.34 (EES versus PES; $P<0.0001$). There was a lower risk of cardiac death or myocardial with EES compared with PES (hazard ratio, 0.65; 95% confidence interval, 0.56–0.75; $P<0.0001$), which was directly related to the lower risk of stent thrombosis–associated events (EES versus PES: hazard ratio, 0.36; 95% confidence interval, 0.23–0.57).

Conclusion—Current treatment with EES is associated with a lower risk of very late stent thrombosis compared with early-generation drug-eluting stents. **(*Circulation*. 2012;125:1110-1121.)**

Key Words: drug-eluting stents ■ registries ■ thrombosis

Stent thrombosis (ST) is a rare but devastating complication after coronary stent implantation; it may lead to death or myocardial infarction (MI) in up to 90% of cases.[1–3] Whereas early ST (0–30 days) and late ST (31–360 days) occur with similar frequency among patients treated with bare metal and early-generation drug-eluting stents (DES),[4–6] very late ST (VLST) emerged as a distinct entity complicating the use of early-generation DES releasing sirolimus (SES) or paclitaxel (PES) with a steady annual risk of 0.5% to 0.6% up to 5 years.[7,8] Mechanisms leading to VLST are distinct from those responsible for early or late ST. The persistence of uncovered struts with evidence of chronic inflammation and fibrin deposition leading to positive remodeling and strut malapposition was the hallmarks of thrombosed stent segments in postmortem and intracoronary imaging studies.[7–11] The durable polymer matrix, the dose of the antiproliferative drug, and its release kinetics have been incriminated as a likely trigger of delayed healing and chronic inflammation leading to these late adverse events.[12,13]

Editorial see p 1078
Clinical Perspective on p 1121

Newer-generation DES have been developed to improve the safety profile by means of more biocompatible polymers,

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reduced drug dose with adapted release kinetics, and reduced strut thickness. Newer-generation DES releasing everolimus (EES) have been shown to improve safety and efficacy compared with PES in several randomized clinical trials.[14,15] Conversely, direct comparison of EES with SES up to 1 year yielded similar results in terms of safety and efficacy in several trials,[16–21] including the synthesis of these results in a recently published meta-analysis.[22] So far, these studies have been limited in size with maximal follow-up to only 2 years, and none of the studies specifically addressed the end point of VLST in a large patient population with the unrestricted use of DES. The latter is important because VLST became apparent mainly in all-comers studies with the inclusion of complex patient and lesion characteristics, and VLST constitutes the principal shortcoming of early-generation DES. We previously reported the incidence of ST in a cohort of patients treated with the unrestricted use of SES and PES at 2 academic institutions. For the purpose of the present study, we extended the cohort to include all patients treated with EES and compared the incidence of ST and particularly VLST between the 3 stent types during follow-up through 4 years.

Methods

Patient Population

Between November 1, 2006, and March 31, 2009, a total of 4212 patients underwent percutaneous coronary intervention (PCI) with EES (XIENCE V, Abbott Vascular, Santa Clara, CA; or PROMUS, Boston Scientific, Natick, MA) at 2 academic referral hospitals in the Netherlands and Switzerland. In the Dutch institution, EES have been used as a default strategy for PCI as part of the XIENCE Stent Evaluated at Rotterdam Cardiology Hospital (X-SEARCH) registry since March 1, 2007, until the end of this study. In the Swiss institution, EES have been used since November 1, 2006, and implanted on a daily basis alternating with biolimus-eluting stents and zotarolimus-eluting stents. Patients who had been treated with different DES within the same patient were excluded from the current registry. Between April 16, 2002, and December 31, 2005, a total of 8146 consecutive patients underwent coronary intervention with SES or PES, of whom 3882 were treated with SES (Cypher, Cordis Corp, Johnson & Johnson, Warren, NJ) and 4323 were treated with PES (TAXUS, Express, or Liberté, Boston Scientific). The individual use of both stent types at the 2 centers has been described in detail elsewhere.[23] The study was approved by the local ethics committee at both institutions and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Data Collection

All patients were actively followed up for major adverse cardiac events by the use of patient-administered postal questionnaires including questions on rehospitalization and major adverse cardiac events. This was complemented by a search of hospital databases of the 2 institutions. In Bern, the last follow-up took place beginning on February 1, 2007, for patients who had undergone implantation of SES or PES and beginning on February 1, 2010, for patients with EES. In Rotterdam, the last follow-up took place beginning on July 1, 2005, for patients with PES; on July 1, 2006, for patients with SES; and on April 1, 2010, for patients with EES. Vital status was ascertained from hospital records and municipal civil registries. For patients with a suspected event, relevant medical records, discharge letters, and coronary angiography documentation were systematically collected. All suspected clinical events were adjudicated by local cardiologists affiliated with the 2 institutions, whereas all ST events were adjudicated by an independent clinical event committee; the committee members were unaware of the type of stent implanted. Baseline clinical and procedural characteristics and all follow-up data were entered into a dedicated database held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland) that was responsible for central data audits and maintenance of the database.

Procedures

EES were available in diameters from 2.25 to 4.0 mm and in lengths from 8 to 28 mm; SES were available in diameters from 2.25 to 3.5 mm and in lengths from 8 to 33 mm; and PES were available in diameters from 2.25 to 4.0 mm and in lengths from 8 to 32 mm. The procedure and treatment, including periprocedural and postprocedural medication regimen, were performed according to current practice guidelines. All patients, regardless of stent type, received a loading dose of clopidogrel 300 to 600 mg during or immediately after the procedure and were prescribed lifelong once-daily aspirin. In the Dutch institution, clopidogrel was administered for at least 3 months to patients with SES and for at least 6 months if patients had received $\geq$3 stents, if the total stent length was $>$36 mm, or if a chronic total occlusion or bifurcation was treated. Dutch patients treated with PES received clopidogrel for at least 6 months, whereas EES patients were prescribed clopidogrel for 12 months. In the Swiss institution, all patients were prescribed clopidogrel for a duration of at least 12 months regardless of stent type. The use of glycoprotein IIb/IIIa antagonists was left to the discretion of the operator.

Definitions

The primary end point was definite ST up to a maximum follow-up of 4 years. ST was defined according to the Academic Research Consortium (ARC)[24] and reported separately for the early (0–30 days), late (31–360 days), and very late ($>$360 days) time periods. The definition of cardiac death included any deaths with an immediate cardiac cause, procedure-related deaths, unwitnessed deaths, and deaths with an unknown cause. The diagnosis of MI was based on an elevation in creatine kinase to more than twice the upper limit of normal and an elevation of creatine kinase-MB to $>$3 times the upper limit of normal in the presence of ischemic symptoms or ischemic ECG changes. A 12-lead ECG was obtained before the procedure and within 24 hours after PCI. Additional ECGs were obtained in case of recurrent signs or symptoms of ischemia. Risk factors and comorbidities in each patient were determined as classified by the treating physician. Acute coronary syndrome was defined as acute myocardial ischemia on the basis of clinical symptoms, ECG changes, and elevation of cardiac biomarkers and encompasses acute ST-segment–elevation MI, non–ST-segment–elevation MI, and unstable angina. Definitions of hypertension, hyperlipidemia, and renal dysfunction were previously reported.[23]

Statistical Analysis

Baseline and procedural variables among the 3 stent types are presented as counts and percentages for dichotomous variables and as mean and SD for continuous variables. Comparisons between groups among dichotomous variables were performed with the Pearson χ^2 test and the Student t test for continuous variables. We calculated incidence rates per 100 patient-years as the number of new events occurring during a specific time period divided by the total number of patient-years actually observed. In contrast to crude percentages, incidence rates take into account differences in the follow-up duration between stent types. Univariable and multivariable Cox proportional hazard regression models were used to assess hazard ratios (HRs) with 95% confidence intervals (CIs) for comparing each of the early-generation DES with EES. For each center, we estimated propensity scores for receiving EES using a logit model that included age, sex, and pretreatment variables associated with stent selection at $P<0.10$: family history of coronary artery disease, acute coronary syndrome, and cardiogenic shock for both centers; body

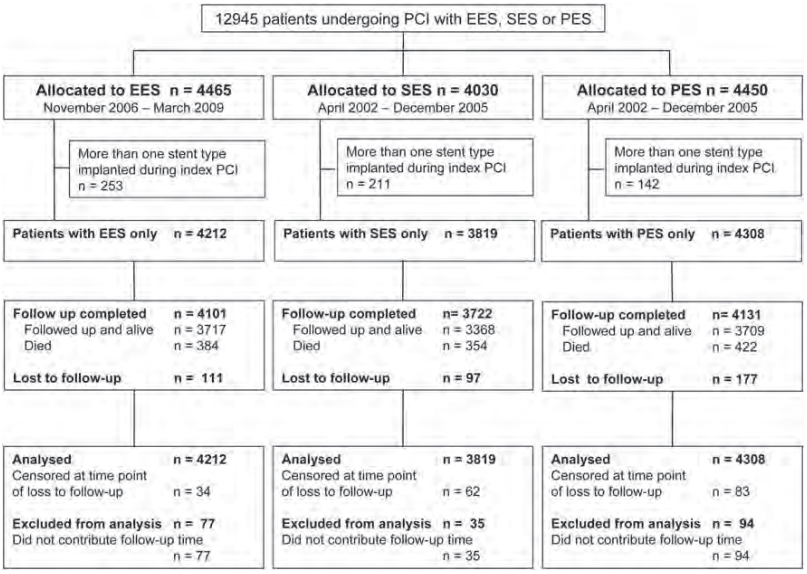


Figure 1. Flow of patients according to Consolidated Standards of Reporting Trials (CONSORT). PCI indicates percutaneous coronary intervention; EES, everolimus-eluting stents; SES, sirolimus-eluting stents; and PES, paclitaxel-eluting stents.

mass index and left ventricular ejection fraction as additional variables for Bern; and arterial hypertension, smoking, diabetes mellitus, and hyperlipidemia for Rotterdam. Propensity scores were used to derive the inverse probability of treatment weights, with the inverse of the propensity score as analytic weights in EES patients and the inverse of 1 minus the propensity score in early-generation DES patients. Comparisons between stents were performed with a Cox proportional hazards model, both crude and adjusted with the inverse probability of treatment weighting. Then, we used landmark analyses according to a prespecified landmark point at 1 year (360 days) and estimated HRs and cumulative incidence rates separately for events up to 1 year and beyond. Stratified analyses were performed according to prespecified baseline characteristics and accompanied by a χ^2 test to assess the interaction between treatment effect and these characteristics. Next, we classified the composite outcome of cardiac death or MI according to the association of outcome events with definite ST, accompanied by a test for difference in log HRs of the composite outcome of cardiac death or MI between outcome events associated with definite ST and outcome events not associated with definite ST. Events occurring 7 days before or after a definite ST were thought to be associated with definite ST for the purpose of this analysis. Statistical analyses were performed with STATA release 11.1 (Stata Corp, College Station, TX). All *P* values are 2 sided.

Results

Between April 16, 2002, and March 31, 2009, 12 339 consecutive patients underwent PCI with EES (4212), SES (3819), and PES (4308; Figure 1). A total of 11 954 patients (96.9%) completed the last follow-up, with 4101 patients receiving EES (97.4%), 3722 patients receiving SES (97.5%), and 4131 patients receiving PES (95.9%). The median follow-up duration among surviving patients completing the last follow-up was 2.5 years in patients treated with EES (interquartile range [IQR], 1.8–3.1 years), 4.0 years in patients treated with SES (IQR, 3.0–4.0 years), and 3.0 years in patients treated with PES (IQR, 2.1–3.6 years) with an accumulated 9519, 12 478, and 10 795 patient-years, respectively.

Baseline clinical characteristics are summarized in Table 1. Patients treated with EES compared with either SES or PES were older, were more frequently hypertensive, smoked less frequently, had a lower left ventricular ejection fraction, and presented more frequently with ST-segment–elevation MI and cardiogenic shock. Patients treated with EES compared with those treated with PES had a higher body mass index, more often had diabetes mellitus, and were more frequently dyslipidemic. Procedural characteristics are shown in Table 2. Compared with patients receiving SES and PES, a higher number of lesions were treated among patients undergoing PCI with EES. The frequency of multivessel treatment, the total stent length, and the number of implanted stents were similar among patients treated with EES and SES but higher among patients treated with PES. Among patients receiving EES compared with PES, a higher proportion of patients underwent revascularization of the left main coronary artery, and a higher number of saphenous vein graft interventions were performed.

Stent Thrombosis

Crude and adjusted outcomes for the primary end point of ARC definite ST and ARC definite or probable ST are shown

Table 1. Baseline Clinical Characteristics

	EES	SES	PES	EES vs SES *P*	EES vs PES *P*	SES vs PES *P*
Total, n	4212	3819	4308			
Age, mean±SD, y	64.3±12	62.5±11.5	62.7±11.6	<0.0001	<0.0001	0.3044
Male sex, n (%)	3083 (73.2)	2856 (74.8)	3192 (74.1)	0.11	0.35	0.48
BMI, mean±SD, kg/m^2	27.2±4.3	27.2±4.2	27±4	0.98	0.02	0.02
Hypertension, n (%)	2384 (56.6)	1966 (51.5)	1778 (41.3)	<0.0001	<0.0001	<0.0001
Family history of CAD, n (%)	1423 (33.8)	1111 (29.1)	1166 (27.1)	<0.0001	<0.0001	0.04
Current smoking, n (%)	1551 (36.8)	1750 (45.8)	1304 (30.3)	<0.0001	<0.0001	<0.0001
Dyslipidemia, n (%)	2272 (53.9)	2086 (54.6)	1990 (46.2)	0.54	<0.0001	<0.0001
Diabetes mellitus, n (%)	807 (19.2)	696 (18.2)	618 (14.3)	0.28	<0.0001	<0.0001
Renal failure (GFR <60 mL/min),* n (%)	182 (11.2)	332 (12)	157 (11.5)	0.46	0.8093	0.66
Renal failure (creatinine >150 μmol/L),* n (%)	49 (3)	81 (2.9)	39 (2.9)	0.85	0.79	0.91
Left ventricular ejection fraction <50%,* n (%)	549 (33.8)	744 (26.8)	339 (24.8)	<0.0001	<0.0001	0.17
Acute coronary syndrome, n (%)	2642 (62.7)	2016 (52.8)	2543 (59)	<0.0001	0.0004	<0.0001
Unstable angina/non–ST-segment–elevation MI	1105 (41.8)	1042 (56.6)	1151 (45.3)			
ST-elevation–elevation MI	1537 (58.2)	874 (43.4)	1388 (54.7)			
Cardiogenic shock, n (%)	130 (3.1)	58 (1.5)	66 (1.5)	<0.0001	<0.0001	0.96

EES indicates everolimus-eluting stent patients; SES, sirolimus-eluting stent patients; PES, paclitaxel-eluting stent patients; BMI, body mass index; CAD, coronary artery disease; GFR, glomerular filtration rate; and MI, myocardial infarction. Data are presented as mean±SD when appropriate. Comparisons between groups among dichotomous variables were performed with the Pearson χ^2 test and Student *t* test for continuous variables.

*Data available only in Bern patients.

in Table 3 and Figures 2 and 3. At 4 years, the incidence rate of ARC definite ST per 100 person-years was lower among EES-treated patients (1.4) compared with SES-treated patients (2.9; adjusted HR, 0.41; 95% CI, 0.27–0.62; $P<0.0001$) and PES-treated patients (4.4; adjusted HR, 0.33; 95% CI, 0.23–0.48; $P<0.0001$) in adjusted analyses. Differences in terms of ARC definite VLST per 100 person-years (incidence rate) were particularly pronounced, with an incidence rate of 0.6 in EES, 1.4 in SE, and 2.4 in PES, resulting in a relative risk reduction of 67% when EES is compared with SES and 76% when EES is compared with PES. The annual incidence rate of VLST amounted to 0.8 for PES (95% CI, 0.2–0.4), 0.5 for SES (95% CI, 0.4–0.7), and 0.2 for EES (95% CI, 0.1–0.5). The findings of the primary end point of ARC definite ST were consistent in stratified analyses across major subgroups including age, sex, diabetes mellitus, acute coronary syndromes, left ventricular function, number of stents, and stent diameter and length (Figure 4). Similar to the primary outcome measures, incidence rates were consistently lower for the secondary end point of ARC definite or probable ST during the overall time period and beyond 1 year (very late definite or probable ST; Table 3 and Figure 3).

Death and MI

Crude and adjusted outcomes of major ischemic end points, including death, cardiac death, and MI, are summarized in Table 4. In crude analyses, the risk of cardiac death was lowest with SES (unadjusted HR, 1.67; 95% CI, 1.24–2.26; $P=0.002$) and similar for EES and PES (unadjusted HR, 0.96; 95% CI, 0.81–1.14; $P=0.65$). After adjustment, there was no difference in the risk of cardiac death for the comparison of EES with SES (adjusted HR, 1.03; 95% CI, 0.84–1.26; $P=0.79$) but a decreased risk for the comparison of EES with PES (adjusted HR, 0.79; 95% CI, 0.66–0.94; $P=0.007$). EES were associated with a lower adjusted risk of MI compared with SES (adjusted HR, 0.66; 95% CI, 0.51–0.86; $P=0.002$) and PES (adjusted HR, 0.47; 95% CI, 0.37–0.60; $P<0.0001$). There was a trend toward a lower risk of cardiac death or MI compared with SES (adjusted HR, 0.86; 95% CI, 0.74–1.02; $P=0.077$) and significantly lower risk of cardiac death or MI compared with PES (adjusted HR, 0.65; 95% CI, 0.56–0.75; $P<0.0001$).

Figure 5 presents analyses of the composite of cardiac death or MI and of cardiac death associated with definite ST (Figure 5A) and not associated with definite ST (Figure 5B) for the 3 different stent types. Cardiac death or MI associated with definite ST was less frequent with EES than SES (adjusted HR, 0.46; 95% CI, 0.26–0.81) and PES (adjusted HR, 0.36; 95% CI, 0.23–0.57; Figure 5A), whereas there was little evidence for a difference in cardiac death or MI occurring in the absence of definite ST between stent types (EES versus SES: adjusted HR, 1.00; 95% CI, 0.84–1.20; and EES versus PES: adjusted HR, 0.76; 95% CI, 0.64–0.89; Table I in the online-only Data Supplement and Figure 5B). A formal test for differences in the log HRs of the composite outcome of cardiac death or MI between outcome events associated with definite ST and outcome events not associated with definite ST was positive for both crude and adjusted analyses (P for difference ≤ 0.01; see Table I in the online-only Data Supplement). We observed no difference between stent types and the risk of cardiac death regardless of the association with or without definite ST.

Cardiovascular medications at baseline and at latest follow-up are shown in Table II in the online-only Data Supplement. The time point of assessment for cardiovas-

Table 2. Procedural Characteristics

	EES	SES	PES	EES vs SES *P*	EES vs PES *P*	SES vs PES *P*
Total, n	4212	3819	4308			
Multivessel treatment, n (%)	686 (16.3)	653 (17.2)	806 (18.7)	0.29	0.003	0.07
Vessels treated per patient, mean±SD, n	1.2±0.4	1.2±0.4	1.2±0.4	0.21	0.66	0.09
Lesions treated per patient, mean±SD, n	1.8±1	1.5±0.7	1.4±0.7	<0.0001	<0.0001	0.45
1, n (%)	821 (50.6)	1777 (64.4)	885 (64.8)			
2, n (%)	473 (29.2)	736 (26.7)	381 (27.9)			
3, n (%)	218 (13.4)	202 (7.3)	80 (5.9)			
≥4, n (%)	110 (6.8)	38 (1.4)	19 (1.4)			
Target vessel, n patients (%)						
Left main	179 (4.2)	90 (2.4)	152 (3.5)	<0.0001	0.08	0.002
Left anterior descending	2077 (49.3)	1915 (50.3)	2130 (49.4)	0.36	0.90	0.42
Left circumflex	1099 (26.1)	952 (25)	1121 (26)	0.27	0.94	0.31
Right coronary artery	1472 (34.9)	1291 (33.9)	1614 (37.5)	0.34	0.02	0.0009
Arterial bypass graft, n (%)	4 (0.1)	7 (0.2)	6 (0.1)	0.28	0.55	0.61
Saphenous vein graft, n (%)	127 (3)	103 (2.7)	58 (1.3)	0.41	<0.0001	<0.0001
Stents per patient, mean±SD, n	1.9±1.2	1.9±1.1	2±1.3	0.01	0.0004	<0.0001
Average stent diameter, mean±SD, mm	3.0 (±0.4)	2.9 (±0.5)	3.0 (±0.4)	<0.0001	0.03	<0.0001
Total stent length per patient, mean±SD, mm	33.1 (±23.4)	33.7 (22.9)	38.5 (28.2)	0.27	<0.0001	<0.0001
Glycoprotein IIb/IIIa antagonist, n (%)	895 (21.2)	733 (19.3)	755 (17.7)	0.03	<0.0001	0.07
Aspirin at discharge, n (%)	4028 (98.7)	3687 (98.9)	4043 (98.3)	0.36	0.10	0.01
Clopidogrel at discharge, n (%)	4048 (99.2)	3704 (99.8)	4095 (99.4)	0.0003	0.17	0.02
Oral anticoagulation at discharge, n (%)	72 (1.8)	87 (2.3)	130 (3.1)	0.08	0.0001	0.04

EES indicates everolimus-eluting stent patients; SES, sirolimus-eluting stent patients; and PES, paclitaxel-eluting stent patients. Data are presented as mean±SD when appropriate. Comparisons between groups for dichotomous variables were performed with the Pearson χ^2 test and Student *t* test for continuous variables. The number of patients on discharge medication is based on the number of patients alive at discharge.

cular medications at the latest follow-up differed among groups (EES, 2.38 years [IQR, 1.6–3.0 years]; SES, 3.6 years [IQR, 2.8–4.0 years]; PES, 4.0 years [IQR 3.4–4.0 years]). The overall number of patients on dual antiplatelet therapy at the time of latest follow-up was low in all 3 groups (EES, 24,1% at 2.38 years; SES, 16.4% at 3.6 years; PES, 13.7% at 4.0 years). In addition, there were no differences in the proportion of patients on dual antiplatelet therapy at the time point of ARC definite ST between stent types ($P=0.66$), as shown in Table III in the online-only Data Supplement. The follow-up was not complete in EES and PES. To test whether the incompleteness of follow-up beyond 2 years influenced results, we performed a sensitivity analysis limited to patients with complete follow-up beyond 2 years and found robust results (Table IV in the online-only Data Supplement).

Table 3. Academic Research Consortium Definite and Definite or Probable Stent Thrombosis Up to 4 Years

				Crude Analysis				Adjusted Analysis			
				EES vs SES		EES vs PES		EES vs SES		EES vs PES	
	EES	SES	PES	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Definite ST											
Early	25 (0.6)	37 (1.0)	54 (1.3)	0.62 (0.38–1.03)	0.07	0.47 (0.29–0.76)	0.002	0.53 (0.30–0.93)	0.03	0.50 (0.31–0.83)	0.006
Late	5 (0.1)	11 (0.3)	27 (0.7)	0.42 (0.15–1.22)	0.11	0.19 (0.07–0.48)	0.0006	0.29 (0.09–0.94)	0.04	0.17 (0.06–0.44)	0.0003
Very late	12 (0.6)	49 (1.6)	53 (2.4)	0.35 (0.18–0.66)	0.001	0.27 (0.15–0.51)	0.0001	0.33 (0.15–0.72)	0.006	0.24 (0.13–0.47)	<0.0001
Overall	42 (1.4)	97 (2.9)	134 (4.4)	0.48 (0.33–0.69)	0.0001	0.34 (0.24–0.48)	<0.0001	0.41 (0.27–0.62)	<0.0001	0.33 (0.23–0.48)	<0.0001
Definite/probable ST											
Early	162 (3.9)	126 (3.3)	203 (4.8)	1.22 (0.97–1.54)	0.09	0.84 (0.68–1.03)	0.09	0.91 (0.71–1.18)	0.48	0.70 (0.57–0.87)	0.001
Late	16 (0.4)	24 (0.7)	59 (1.5)	0.62 (0.33–1.17)	0.14	0.27 (0.16–0.47)	<0.0001	0.46 (0.24–0.89)	0.02	0.24 (0.13–0.41)	<0.0001
Very late	36 (2.0)	86 (2.8)	95 (4.0)	0.63 (0.42–0.93)	0.02	0.45 (0.30–0.66)	<0.0001	0.63 (0.39–1.01)	0.05	0.40 (0.27–0.61)	<0.0001
Overall	214 (6.3)	236 (6.8)	357 (10.1)	0.95 (0.79–1.15)	0.60	0.62 (0.53–0.74)	<0.0001	0.78 (0.63–0.95)	0.02	0.55 (0.46–0.65)	<0.0001

EES indicates everolimus-eluting stent patients; SES, sirolimus-eluting stent patients; PES, paclitaxel-eluting stent patients; HR, hazard ratio; CI, confidence interval; and ST, stent thrombosis. Clinical outcome numbers are expressed as counts and incidence rates per 100 patient-years. Crude HRs were calculated with Cox proportional hazard models. Adjusted risk ratios were calculated with the inverse probability of treatment weights as analytical weighting in Cox proportional hazards models stratified by center.

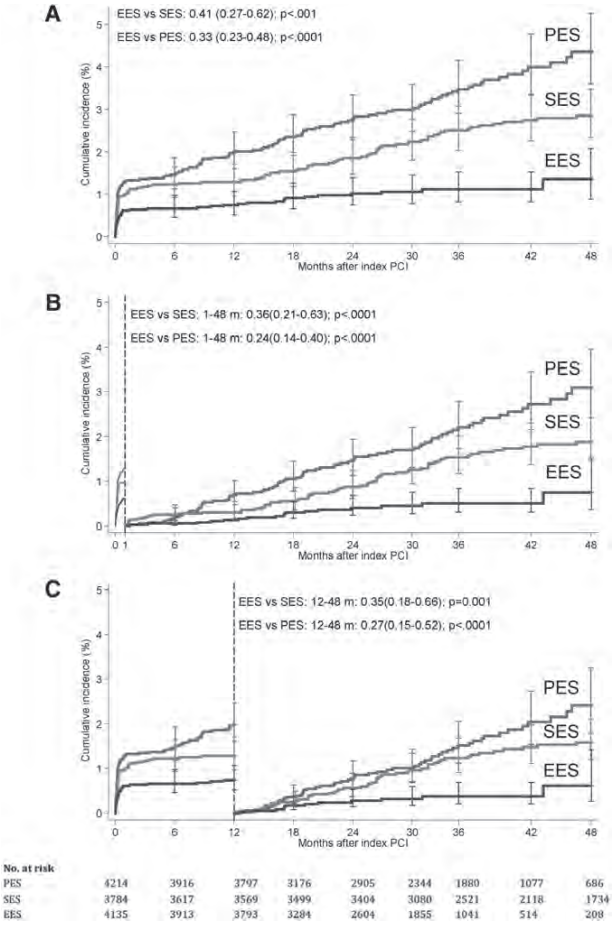


Figure 2. Definite stent thrombosis (ST) in a cohort of patients who received everolimus-eluting stents (EES), sirolimus-eluting stents (SES), or paclitaxel-eluting stents (PES). The Kaplan-Meier curves show the cumulative incidence of definite ST up to 4 years (**A**) with a landmark analysis up to 30 days (**B**), 31 days to 1 year (**B**), and beyond 1 year (**C**). *P* values and hazard ratios are from Cox proportional hazards models. Confidence interval bars indicated every 6 months. ARC indicates Academic Research Consortium.

Discussion

In this large, observational cohort study of all-comers patients treated with the unrestricted use of DES who were followed up for up to 4 years, newer-generation EES reduced the overall risk of ARC definite ST by 58% compared with early-generation SES and by 68% compared with PES. The benefit in favor of EES was most pronounced during the very late period (>1 year), with a 67% and 76% reduced risk of definite ST compared with SES and PES, respectively, resulting in an important reduction of the risk of VLST with the use of EES.

Our findings are consistent with the 2-year outcomes of the randomized Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers (COMPARE) trial comparing newer-generation EES with early-generation PES in an all-comers patient population.[25] Compared with PES, the overall risk of definite ST was lowered by 63% with the use of EES, whereas the risk of VLST was lowered by 77% between 1 and 2 years of follow-up. In the randomized Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With De Novo Native Coronary Artery Lesions (SPIRIT) IV trial comparing EES with PES, the overall risk of definite ST at 2 years was also lowered by 64% in favor of EES, whereas the risk of VLST was nonsignificantly reduced by 24% during the very late period (>1 year).[26] The latter observation is most likely related to differences in patient populations because the phenomenon of VLST emerged among more complex patients and lesions. Although the duration of dual antiplatelet therapy was longer

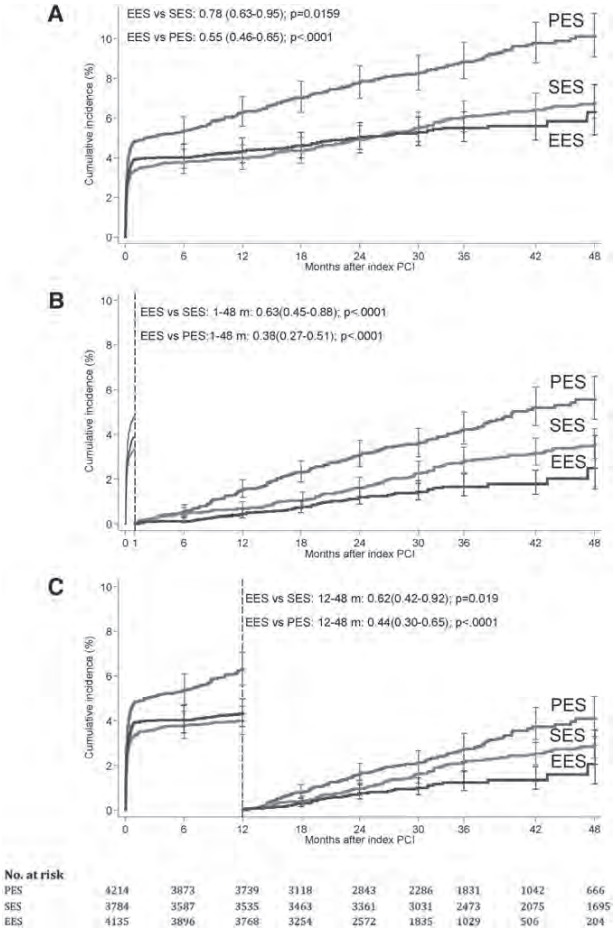
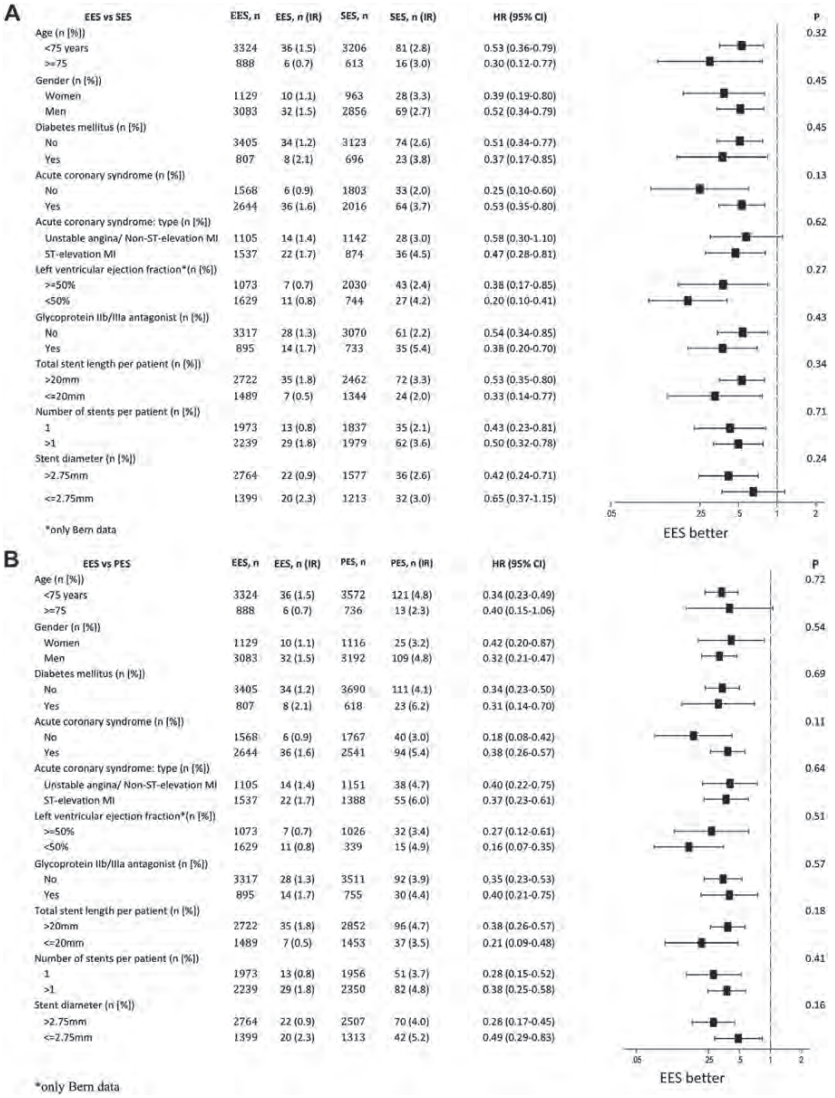


Figure 3. Definite or probable stent thrombosis (ST) in a cohort of patients who received everolimus-eluting stents (EES), sirolimus-eluting stents (SES), or paclitaxel-eluting stents (PES). The Kaplan-Meier curves show the cumulative incidence of definite or probable ST up to 4 years (**A**) with a landmark analysis up to 30 days (**B**), 31 days to 1 year (**B**), and beyond 1 year (**C**). *P* values and hazard ratios are from Cox proportional hazards models. Confidence interval bars are indicated every 6 months. ARC indicates Academic Research Consortium.

in SPIRIT IV compared with COMPARE and may have influenced outcomes, it remains to be shown whether prolonged dual antiplatelet therapy effectively prevents VLST. The present study adds substantially to the available evidence of the risk of VLST with newer-generation DES by extending the follow-up observation to 4 years in the largest patient population treated with EES so far. Because all consecutive patients treated with EES, SES, or PES were included in the present study, this cohort provides a high degree of generalizability to routine clinical practice in experienced centers. Moreover, our study is not limited to the comparison of EES with PES but also provides long-term evidence for the comparison between EES and SES, demonstrating a similar reduction in the risk of overall ST and VLST in favor of EES. Available evidence from randomized trials comparing EES with SES is still limited and based on 1-year data. In a recent meta-analysis of data up to 1 year, however, de Waha et al[22] reported on the composite of definite or probable ST and found a 22% relative risk reduction, even though CIs were wide and overlapped the line of no difference. These midterm results are in line with our long-term results on the same outcome, with a 22% relative risk reduction (95% CI, 0.63–0.95). The robustness of the present analysis is further substantiated by the consistent findings in stratified analyses across major subgroups for the comparison of EES with SES and PES.

Although early-generation SES and PES showed the well-established ongoing risk of VLST with an annual rate of 0.6% to 0.7%, the risk of VLST associated with EES in the present study was comparable to published long-term data on bare



A

EES vs SES	EES, n	EES, n (IR)	SES, n	SES, n (IR)	HR (95% CI)	P
Age (n [%])						0.32
<75 years	3324	36 (1.5)	3206	81 (2.8)	0.53 (0.36-0.79)	
>=75	888	6 (0.7)	613	16 (3.0)	0.30 (0.12-0.77)	
Gender (n [%])						0.45
Women	1129	10 (1.1)	963	28 (3.3)	0.39 (0.19-0.80)	
Men	3083	32 (1.5)	2856	69 (2.7)	0.52 (0.34-0.79)	
Diabetes mellitus (n [%])						0.45
No	3405	34 (1.2)	3123	74 (2.6)	0.51 (0.34-0.77)	
Yes	807	8 (2.1)	696	23 (3.8)	0.37 (0.17-0.85)	
Acute coronary syndrome (n [%])						0.13
No	1568	6 (0.9)	1803	33 (2.0)	0.25 (0.10-0.60)	
Yes	2644	36 (1.6)	2016	64 (3.7)	0.53 (0.35-0.80)	
Acute coronary syndrome: type (n [%])						0.62
Unstable angina/ Non-ST-elevation MI	1105	14 (1.4)	1142	28 (3.0)	0.58 (0.30-1.10)	
ST-elevation MI	1537	22 (1.7)	874	36 (4.5)	0.47 (0.28-0.81)	
Left ventricular ejection fraction*(n [%])						0.27
>=50%	1073	7 (0.7)	2030	43 (2.4)	0.38 (0.17-0.85)	
<50%	1629	11 (0.8)	744	27 (4.2)	0.20 (0.10-0.41)	
Glycoprotein IIb/IIIa antagonist (n [%])						0.43
No	3317	28 (1.3)	3070	61 (2.2)	0.54 (0.34-0.85)	
Yes	895	14 (1.7)	733	35 (5.4)	0.38 (0.20-0.70)	
Total stent length per patient (n [%])						0.34
>20mm	2722	35 (1.8)	2462	72 (3.3)	0.53 (0.35-0.80)	
<=20mm	1489	7 (0.5)	1344	24 (2.0)	0.33 (0.14-0.77)	
Number of stents per patient (n [%])						0.71
1	1973	13 (0.8)	1837	35 (2.1)	0.43 (0.23-0.81)	
>1	2239	29 (1.8)	1979	62 (3.6)	0.50 (0.32-0.78)	
Stent diameter (n [%])						0.24
>2.75mm	2764	22 (0.9)	1577	36 (2.6)	0.42 (0.24-0.71)	
<=2.75mm	1399	20 (2.3)	1213	32 (3.0)	0.65 (0.37-1.15)	

*only Bern data

B

EES vs PES	EES, n	EES, n (IR)	PES, n	PES, n (IR)	HR (95% CI)	P
Age (n [%])						0.72
<75 years	3324	36 (1.5)	3572	121 (4.8)	0.34 (0.23-0.49)	
>=75	888	6 (0.7)	736	13 (2.3)	0.40 (0.15-1.06)	
Gender (n [%])						0.54
Women	1129	10 (1.1)	1116	25 (3.2)	0.42 (0.20-0.87)	
Men	3083	32 (1.5)	3192	109 (4.8)	0.32 (0.21-0.47)	
Diabetes mellitus (n [%])						0.69
No	3405	34 (1.2)	3690	111 (4.1)	0.34 (0.23-0.50)	
Yes	807	8 (2.1)	618	23 (6.2)	0.31 (0.14-0.70)	
Acute coronary syndrome (n [%])						0.11
No	1568	6 (0.9)	1767	40 (3.0)	0.18 (0.08-0.42)	
Yes	2644	36 (1.6)	2541	94 (5.4)	0.38 (0.26-0.57)	
Acute coronary syndrome: type (n [%])						0.64
Unstable angina/ Non-ST-elevation MI	1105	14 (1.4)	1151	38 (4.7)	0.40 (0.22-0.75)	
ST-elevation MI	1537	22 (1.7)	1388	55 (6.0)	0.37 (0.23-0.61)	
Left ventricular ejection fraction*(n [%])						0.51
>=50%	1073	7 (0.7)	1026	32 (3.4)	0.27 (0.12-0.61)	
<50%	1629	11 (0.8)	339	15 (4.9)	0.16 (0.07-0.35)	
Glycoprotein IIb/IIIa antagonist (n [%])						0.57
No	3317	28 (1.3)	3511	92 (3.9)	0.35 (0.23-0.53)	
Yes	895	14 (1.7)	755	30 (4.4)	0.40 (0.21-0.75)	
Total stent length per patient (n [%])						0.18
>20mm	2722	35 (1.8)	2852	96 (4.7)	0.38 (0.26-0.57)	
<=20mm	1489	7 (0.5)	1453	37 (3.5)	0.21 (0.09-0.48)	
Number of stents per patient (n [%])						0.41
1	1973	13 (0.8)	1956	51 (3.7)	0.28 (0.15-0.52)	
>1	2239	29 (1.8)	2350	82 (4.8)	0.38 (0.25-0.58)	
Stent diameter (n [%])						0.16
>2.75mm	2764	22 (0.9)	2507	70 (4.0)	0.28 (0.17-0.45)	
<=2.75mm	1399	20 (2.3)	1313	42 (5.2)	0.49 (0.29-0.83)	

*only Bern data

Figure 4. Subgroup analyses of the primary end point. Subgroup analyses are shown, with the relative risks and 95% confidence intervals (CIs), for the primary end point of Academic Research Consortium definite stent thrombosis throughout 4 years among major subgroups. The *P* value is for interaction between subgroups and treatment effects. **A**, Comparison of everolimus-eluting stents (EES) with sirolimus-eluting stents (SES). **B,** Comparison of EES with paclitaxel-eluting stents (PES). Hazards <1 are in favor of EES. HR indicates hazard ratio; MI, myocardial infarction.

metal stents through 4 years.[6] The reduction of VLST is particularly important because the increased risk of VLST with early-generation DES stirred a debate regarding the need of prolonged dual antiplatelet therapy.[27] Because of the low rate of VLST observed with EES with a prescription time for clopidogrel that was limited to 1 year and the relatively low number of EES patients on dual antiplatelet therapy at the time of last follow-up (24.1%), it appears unlikely that a

Table 4. Clinical Outcomes Up to 4 Years

				Crude Analysis				Adjusted Analysis			
				EES vs SES		EES vs PES		EES vs SES		EES vs PES	
	EES	SES	PES	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Death											
0 to 30 d	135 (3.2)	79 (2.1)	135 (3.1)	1.56 (1.18–2.06)	0.002	1.02 (0.81–1.30)	0.86	1.03 (0.74–1.42)	0.87	0.86 (0.67–1.10)	0.22
>30 d to 1 y	108 (2.7)	77 (2.1)	127 (3.1)	1.29 (0.97–1.73)	0.09	0.86 (0.67–1.11)	0.25	1.09 (0.79–1.52)	0.59	0.73 (0.56–0.95)	0.02
>1 y to 4 y	141 (6.6)	198 (6.5)	160 (6.5)	1.09 (0.87–1.35)	0.47	1.05 (0.83–1.32)	0.69	0.85 (0.67–1.07)	0.17	0.91 (0.71–1.16)	0.43
0 to 4 y	384 (12.0)	354 (10.3)	422 (12.1)	1.26 (1.09–1.46)	0.002	0.98 (0.85–1.13)	0.79	0.98 (0.83–1.15)	0.77	0.83 (0.72–0.96)	0.01
Cardiac death											
0 to 30 d	124 (2.9)	68 (1.8)	122 (2.8)	1.67 (1.24–2.24)	0.0007	1.04 (0.81–1.33)	0.76	1.13 (0.80–1.59)	0.48	0.86 (0.66–1.12)	0.28
>30 d to 1 y	61 (1.5)	46 (1.2)	70 (1.7)	1.22 (0.83–1.79)	0.31	0.88 (0.63–1.24)	0.48	1.06 (0.69–1.64)	0.78	0.70 (0.49–0.99)	0.04
>1 y to 4 y	70 (3.2)	105 (3.5)	92 (4.0)	1.02 (0.75–1.39)	0.89	0.92 (0.67–1.25)	0.58	0.84 (0.61–1.16)	0.29	0.77 (0.55–1.07)	0.12
0 to 4 y	255 (7.5)	219 (6.4)	284 (8.2)	1.30 (1.08–1.56)	0.005	0.96 (0.81–1.14)	0.65	1.03 (0.84–1.26)	0.79	0.79 (0.66–0.94)	0.007
MI											
0 to 30 d	48 (1.2)	57 (1.5)	82 (1.9)	0.77 (0.52–1.13)	0.1748	0.60 (0.42–0.85)	0.0044	0.69 (0.46–1.03)	0.0663	0.58 (0.40–0.84)	0.004
>30 d to 1 y	20 (0.5)	24 (0.7)	58 (1.5)	0.76 (0.42–1.38)	0.3758	0.34 (0.21–0.57)	<0.0001	0.70 (0.38–1.29)	0.2553	0.32 (0.19–0.54)	<0.0001
>1 y to 4 y	37 (1.9)	88 (2.9)	88 (3.7)	0.61 (0.41–0.90)	0.0135	0.49 (0.34–0.73)	0.0004	0.63 (0.40–0.99)	0.0461	0.48 (0.32–0.72)	0.0004
0 to 4 y	105 (3.5)	169 (5.0)	228 (7.0)	0.70 (0.55–0.89)	0.0043	0.49 (0.39–0.62)	<0.0001	0.66 (0.51–0.86)	0.0023	0.47 (0.37–0.60)	<0.0001
Cardiac death/MI											
0 to 30 d	165 (3.9)	121 (3.2)	199 (4.6)	1.24 (0.98–1.57)	0.0711	0.84 (0.69–1.04)	0.107	0.94 (0.73–1.21)	0.6322	0.73 (0.59–0.91)	0.005
>30 d to 1 y	80 (2.0)	65 (1.8)	119 (3.0)	1.13 (0.81–1.57)	0.4701	0.67 (0.51–0.89)	0.0062	1.01 (0.71–1.44)	0.9521	0.56 (0.42–0.76)	0.0001
>1 y to 4 y	101 (4.9)	185 (6.2)	169 (7.4)	0.81 (0.64–1.04)	0.1041	0.71 (0.55–0.91)	0.0066	0.73 (0.56–0.96)	0.0221	0.62 (0.48–0.81)	0.0004
0 to 4 y	346 (10.5)	371 (10.8)	487 (14.2)	1.04 (0.89–1.20)	0.6269	0.76 (0.66–0.87)	0.0001	0.86 (0.74–1.02)	0.0773	0.65 (0.56–0.75)	<0.0001

EES indicates everolimus-eluting stent patients; SES, sirolimus-eluting stent patients; PES, paclitaxel-eluting stent patients; HR, hazard ratio; CI, confidence interval; and MI, myocardial infarction. Clinical outcome numbers are expressed as counts and incidence rates per 100 patient-years. Crude hazard ratios were calculated with Cox proportional hazard models. Adjusted risk ratios were calculated with the inverse probability of treatment weights as analytical weighting in Cox proportional hazards models stratified by center.

prolonged regimen of dual antiplatelet therapy in patients treated with EES can further improve on stent-related outcomes. This has recently been corroborated by 2 randomized controlled trials showing no reduction in ischemic end points, including ST, when dual antiplatelet therapy is prolonged beyond 6 or 12 months.[28,29]

In our study, >85% of the 273 patients with definite ST suffered the composite of cardiac death or MI compared with a mere 8% of patients without definite ST. The lower risk of definite ST was therefore bound to translate directly into a lower risk of cardiac death or MI with newer-generation EES compared with early-generation SES and PES. Thus, cardiac death or MI associated with definite ST was less frequent with EES than SES and PES (Figure 4A), whereas cardiac death or MI occurring in the absence of definite ST showed a similar risk for all stent types (Figure 4B), providing a mechanistic explanation for the observed safety.

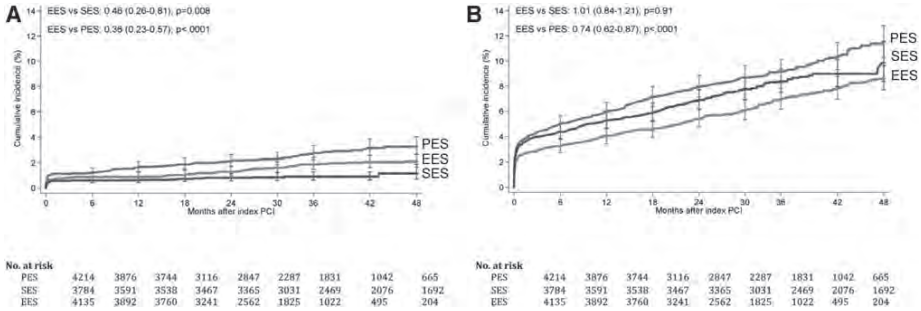


Figure 5. Clinical outcomes according to the presence or absence of an association with definite stent thrombosis (ST). **A**, Cumulative incidence of cardiac death or myocardial infarction (MI) associated with definite ST throughout 4 years. **B**, Cumulative incidence of cardiac death or MI not associated with definite ST throughout 4 years. *P* values shown are derived from unadjusted analysis. Corresponding hazard ratios and *P* for interaction for adjusted and unadjusted analysis are shown in the Table I in the online-only Data Supplement. Confidence bars are indicated every 6 month. PCI indicates percutaneous coronary intervention; EES, everolimus-eluting stents; SES, sirolimus-eluting stents; and PES, paclitaxel-eluting stents.

The mechanisms underlying the lower risk of definite ST with newer-generation EES remain speculative but may be related to the different components of the device. First, the lower strut thickness may result in less arterial injury, may accelerate reendothelialization owing to the lower physical height of the mechanical barrier, and may have a lesser degree of flow disruption, resulting in a lower thrombogenicity.[30,31] Second, it has been suggested that the properties of the fluoropolymer surface (polyvinylidene fluoride-cohexafluoropropylene) reduce thrombogenicity and inflammatory reactions while improving endothelialization.[32] Improved endothelialization has been shown in a comparative study in rabbit iliac arteries showing more rapid reendothelialization with EES compared with SES and PES at 14 days.[33] Third, drug dose and release kinetics may play a role because higher doses not only inhibit endothelialization but also may cause toxic effects within the vessel wall.[34] A nonrandomized study compared the in vivo healing response between EES and SES using optical coherence tomography and reported a lower incidence of uncovered struts (EES, 4.4% versus 10.5%; $P=0.016$) and a lower rate of intracoronary masses compatible with thrombus (5.0% versus 34.3%; $P<0.001$).[35]

Alternative DES platforms such as biodegradable polymer-based DES and fully bioresorbable devices have been developed to further improve the clinical safety and efficacy of PCI. Although it appears difficult to further improve outcomes in terms of VLST, remaining issues such as complex patient populations (those with diabetes mellitus or multivessel disease), lack of vasomotion and remodeling of the stented segment, side-branch access, surgical revascularization of previously stented long segments, and noninvasive imaging will need to be addressed by future-generation devices.

Limitations

The present study has several limitations. This was not a randomized comparison between newer- and early-generation DES; in fact, we observed differences in baseline clinical and procedural characteristics among the 3 groups. However, analyses were adjusted for these differences by the use of inverse probability of treatment weighting, thus minimizing the potential of bias. Moreover, differences in favor of EES were large, consistent across major subgroups, and plausible in that they relate to the benefit in reducing the risk of cardiac death or MI for events associated with ST. The follow-up at 4 years is not complete in the EES and PES groups; however, a sensitivity analysis limited to patients with complete follow-up beyond 2 years (Table IV in the online-only Data Supplement) found the results to be even more in favor of EES, suggesting an important differential in the timing of individual adverse events (Table IV in the online-only Data Supplement). Another limitation is the sequential enrollment period for patients treated with EES compared with SES and PES. We used postal questionnaires to obtain information about possible events complemented by a search of the hospital database at both institutions, which may be considered inferior to telephone follow-up or clinical visits. However, event rates observed with early-generation DES were higher than in many randomized controlled trials or registries and in view of the similar methodology applied for all 3 stent groups, and underreporting of events appears unlikely. Differences in the duration of dual antiplatelet therapy within the first year after DES implantation may have contributed to an improved outcome in patients treated with EES. Although the prescription time was limited to 1 year in all EES patients, we cannot exclude that a higher proportion of EES patients continued the dual antiplatelet therapy beyond 1 year, and this may improve the outcomes observed with EES. However, we report the proportion of patients on dual antiplatelet therapy at the latest follow-up, and the proportions of patients on dual antiplatelet therapy were comparable among the 3 stent types when the different time points of the latest follow-up at which information about dual antiplatelet therapy was assessed were taken into account (24.1% of EES patients on dual antiplatelet therapy at 2.38 years, 16.4% of SES at 3.6 years, and 13.7% of PES patients at 4.0 years). Finally, recent data from 2 randomized controlled trials[28,29] suggest that a prolongation of dual antiplatelet therapy beyond 6 months or 1 year, respectively, does not improve ischemic outcomes, suggesting that potential differences in dual antiplatelet therapy beyond 1 year may not have an impact on the primary outcome measure of ARC definite ST.

We cannot exclude that improvements in interventional treatment strategies over time such as higher implantation pressures, more frequently performed postdilatation, and thrombus aspiration may have contributed to an improved outcome among EES- compared with SES- and PES-treated patients. However, these potential improvements in interventional treatment technique are more likely to affect stent-related outcomes within the first year after stent implantation rather than during the very late time period.

Conclusions

Current treatment with EES is associated with a lower risk of VLST compared with treatment with early-generation DES. The reduction of the risk of VLST with the unrestricted use of EES overcomes the principal limitation of early-generation DES and constitutes an important advance in DES safety.

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CLINICAL PERSPECTIVE

Early-generation drug-eluting stents releasing sirolimus (SES) or paclitaxel (PES) are associated with an increased risk of very late stent thrombosis with an annual incidence of 0.5% to 0.6%. It is unknown whether the risk of very late stent thrombosis persists with newer-generation everolimus-eluting stents (EES). A total of 12 339 patients undergoing treatment with either SES, PES, or EES between 2002 and 2009 were followed up for up to 4 years to compare the incidence of stent thrombosis between stent types with particular focus on very late stent thrombosis. The incidence rate of stent thrombosis through 4 years was lower among EES-treated patients (1.4%) compared with patients treated with SES (2.9%; $P<0.0001$) and PES (4.4%; $P<0.0001$). The reduction in stent thrombosis was most prominent during the very late time period (>1 year) with a 67% (EES versus SES) and 76% (EES versus PES) risk reduction in favor of EES. The annual incidence rate of very late stent thrombosis amounted to 0.2% in EES, 0.5% with SES, and 0.8% with PES. The lower risk of cardiac death or myocardial infarction with EES compared with PES (hazard ratio, 0.67; 95% confidence interval, 0.58–0.77; $P<0.0001$) was directly related to the lower risk of stent thrombosis–associated events. Newer-generation EES improve clinical outcome by reducing the risk of stent thrombosis compared with early-generation drug-eluting stents during long-term follow-up. The important reduction of the risk of very late stent thrombosis with the unrestricted use of EES overcomes the principal limitation of early-generation drug-eluting stents and constitutes an important advance in drug-eluting stent safety.

Supplemental Tables

Supplemental Table 1. Unadjusted and adjusted hazard ratios and p-values for differences in log hazard ratios of the composite outcome of cardiac death or MI between outcome events associated with definite ST and outcome events not associated with definite ST.

	EES vs. SES				EES vs. PES			
	Unadjusted HR (95% CI)	P for difference in HR	Adjusted HR (95% CI)	P for difference in HR	Unadjusted HR (95% CI)	P for difference in HR	Adjusted HR (95% CI)	P for difference in HR
Overall		0.0002				<0.0001		0.003
Associated with ST	0.46 (0.29-0.72)		0.46 (0.26-0.81)	0.01	0.32 (0.21-0.49)		0.36 (0.23-0.57)	
Not associated with ST	1.15 (0.97-1.37)		1.00 (0.84-1.20)		0.88 (0.75-1.04)		0.76 (0.64-0.89)	

Supplemental Table 2. Cardiovascular medication at discharge and follow-up

	EES	SES	PES	EES vs SES p-Value	EES vs PES p-Value	SES vs PES p-Value
Medication at Discharge						
Aspirin (n [%])	4028 (98.7)	3687 (98.9)	4043 (98.3)	0.36	0.1	0.01
Clopidogrel (n [%])	4048 (99.2)	3704 (99.8)	4095 (99.4)	<.001	0.17	0.02
Dual antiplatelet therapy (n [%])	4094 (97.2)	3738 (97.9)	4247 (98.6)	0.15	0.006	0.08
Oral anticoagulation (n [%])	72 (1.8)	87 (2.3)	130 (3.1)	0.08	<.0001	0.04
Betablocker (n [%])	1038 (65.2)	1619 (59.7)	826 (61)	<.0001	0.02	0.41
ACE inhibitor (n [%])	836 (52.5)	1449 (53.4)	704 (52)	0.55	0.81	0.4
AT II inhibitor (n [%])	254 (15.9)	377 (13.9)	207 (15.3)	0.07	0.63	0.23
Calcium antagonist (n [%])	147 (9.2)	279 (10.3)	144 (10.6)	0.26	0.2	0.73
Statin (n [%])	1339 (84.1)	2312 (85.3)	1163 (86)	0.29	0.15	0.55
Oral antidiabetic (n [%])	175 (11)	285 (10.5)	134 (9.9)	0.62	0.34	0.55
Insulin (n [%])	100 (6.3)	157 (5.8)	60 (4.4)	0.51	0.03	0.07
Medication at follow-up						
Mean follow-up duration (IQR)	**2.38 (2.6-4.0)**	**3.63 (2.8-4.0)**	**4.0 (3.4-4.0)**			
Aspirin (n [%])	1193 (93.2)	2101 (87.1)	1012 (86.9)		<0.0001	<0.0001
Clopidogrel (n [%])	365 (28.5)	524 (21.7)	217 (18.6)		<0.0001	<0.0001
Dual antiplatelet therapy (n [%])	309 (24.1)	395 (16.4)	159 (13.7)		<0.0001	<0.0001
Oral anticoagulation (n [%])	51 (4)	197 (8.2)	105 (9)		<0.0001	<0.0001

Betablocker (n [%])	888 (69.4)	1653 (68.8)	792 (68.2)	0.73	0.52
ACE inhibitor (n [%])	538 (42.1)	Na	Na	Na	Na
AT II inhibitor (n [%])	370 (28.9)	Na	Na	Na	Na
Calcium antagonist (n [%])	205 (16)	366 (15.3)	215 (18.5)	0.53	0.1
Statin (n [%])	1087 (84.9)	1843 (79.7)	821 (76.9)	<.0001	<.0001
Oral antidiabetic* (n [%])	153 (12)	Na	Na	Na	Na
Insulin (n [%])	64 (5)	Na	Na	Na	Na

The medication was assessed only in the Bern population with the exception of aspirin, clopidogrel and anticoagulation at discharge. Data are presented as mean (SD) or n (%). Comparisons between groups for dichotomous variables were performed using Pearson's chi square test. Numbers are based on patients alive at discharge and at latest follow-up. Na=not available.

Supplemental Table 3. Antiplatelet therapy at the timepoint of ARC definite stent thrombosis

	All	EES	SES	PES	P-Value
ARC definite ST (n)	273	42	98	133	
Complete data on medication at time of ST (n)	267	42	93	132	
DAPT status					0.66
On DAPT at ST, n(%)	127 (47.9)	23 (56.1)	44 (47.3)	60 (45.8)	
Only Aspirin at ST, n(%)	103 (38.9)	14 (34.2)	33 (35.5)	56 (42.8)	
Only Clopidogrel at ST, n(%)	6 (2.3)	1 (2.4)	2 (2.2)	3 (2.3)	
On neither antiplatelet at ST, n(%)	29 (10.9)	3 (7.3)	14 (15.1)	12 (9.2)	

ARC=academic research consortium, DAPT=dual antiplatelet therapy, ST=stent thrombosis

Supplemental Table 4. Clinical outcomes between 0 and 2 years and between 2 and 4 years.

				Crude Analysis				Adjusted Analysis			
				EES vs. SES		EES vs. PES		EES vs. SES		EES vs. PES	
	EES	SES	PES	HR (95% CI)	P Value	HR (95% CI)	p Value	HR (95% CI)	P Value	HR (95% CI)	p Value
Death											
0 to 2 yrs	322 (8.0)	239 (6.3)	346 (8.4)	1.30 (1.10-1.54)	0.002	0.94 (0.81-1.10)	0.44	1.03 (0.87-1.22)	0.74	0.75 (0.64-0.88)	0.0005
2 to 4 yrs	62 (4.4)	115 (4.3)	76 (4.1)	1.14 (0.83-1.56)	0.43	1.20 (0.85-1.68)	0.30	0.92 (0.67-1.25)	0.58	1.01 (0.71-1.42)	0.97
Cardiac Death											
0 to 2 yrs	223 (5.5)	154 (4.1)	240 (5.8)	1.37 (1.12-1.69)	0.002	0.94 (0.79-1.13)	0.53	1.07 (0.87-1.33)	0.50	0.74 (0.61-0.90)	0.002
2 to 4 yrs	32 (2.1)	65 (2.4)	44 (2.6)	1.01 (0.66-1.56)	0.95	1.09 (0.69-1.73)	0.70	0.83 (0.54-1.26)	0.38	0.91 (0.58-1.44)	0.69
MI											
0 to 2 yrs	93 (2.4)	113 (3.0)	183 (4.6)	0.79 (0.60-1.03)	0.08	0.51 (0.40-0.65)	<.0001	0.76 (0.57-1.01)	0.06	0.51 (0.39-0.66)	<.0001
2 to 4 yrs	12 (1.1)	56 (2.0)	45 (2.4)	0.41 (0.22-0.77)	0.006	0.40 (0.21-0.75)	0.004	0.39 (0.20-0.77)	0.006	0.36 (0.18-0.70)	0.003
Cardiac Death/MI											
0 to 2 yrs	304 (7.5)	255 (6.8)	402 (9.8)	1.13 (0.96-1.34)	0.15	0.76 (0.66-0.88)	0.0003	0.94 (0.79-1.12)	0.49	0.65 (0.55-0.76)	<.0001
2 to 4 yrs	42 (3.2)	116 (4.3)	85 (5.0)	0.72 (0.50-1.02)	0.07	0.73 (0.51-1.06)	0.10	0.62 (0.43-0.89)	0.01	0.62 (0.43-0.91)	0.01
Definite ST											
0 to 2 yrs	39 (1.0)	68 (1.9)	106 (2.8)	0.55 (0.37-0.82)	0.003	0.37 (0.26-0.53)	<.0001	0.48 (0.32-0.72)	0.0004	0.35 (0.24-0.51)	<.0001
2 to 4 yrs	3 (0.3)	29 (1.0)	28 (1.6)	0.20 (0.06-0.65)	0.008	0.17 (0.05-0.55)	0.003	0.19 (0.05-0.66)	0.009	0.15 (0.05-0.52)	0.003

Definite / ProbableST											
0 to 2 yrs	202 (5.1)	183 (4.9)	312 (7.8)	1.04 (0.85-1.27)	0.70	0.65 (0.54-0.78)	<.0001	0.86 (0.70-1.06)	0.15	0.55 (0.46-0.66)	<.0001
2 to 4 yrs	11 (1.3)	52 (1.9)	44 (2.5)	0.42 (0.22-0.81)	0.01	0.37 (0.19-0.73)	0.004	0.42 (0.21-0.84)	0.01	0.35 (0.18-0.71)	0.003

3.3

Long-term invasive follow-up of the everolimus-eluting bioresorbable vascular scaffold: five-year results of multiple invasive imaging modalities.

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Long-term invasive follow-up of the everolimus-eluting bioresorbable vascular scaffold: five-year results of multiple invasive imaging modalities

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KEYWORDS

- bioresorbable vascular scaffold
- percutaneous coronary intervention

Abstract

Aims: Invasive imaging modalities have shown restoration of vasomotion, prevention of restenosis and, most importantly, increase in lumen area between six months and two years after first-generation everolimus-eluting bioresorbable vascular scaffold (Absorb BVS) implantation. Our aim was to assess whether these positive findings were sustained in the long term.

Methods and results: Patients included in the ABSORB cohort A from the Thoraxcenter Rotterdam cohort underwent coronary catheterisation including angiography, intravascular ultrasound (IVUS), virtual histology, optical coherence tomography (OCT) and vasomotion testing at five years. Eight out of 16 patients underwent catheterisation and scaffold assessment with multiple imaging modalities. A trend towards an increase in minimum luminal diameter was observed between two and five years by angiography (1.95±0.37 mm vs. 2.14±0.38 mm; p=0.09). IVUS data showed an increase in mean lumen area at five years (6.96±1.13 mm^2) compared to six months (6.17±0.74 mm^2; p=0.06) and two years (6.56±1.16 mm^2; p=0.12), primarily due to a persistent reduction in plaque area size between six months and five years (9.17±1.86 mm^2 vs. 7.57±1.63 mm^2; p=0.03). The necrotic core area was reduced at five years compared to post-procedural results. In OCT, an increase in mean and minimal luminal area was observed. Moreover, no scaffold struts could be identified and a smooth endoluminal lining was observed. The scaffolded coronary segment did not show signs of endothelial dysfunction with acetylcholine testing.

Conclusions: At five years, the Absorb BVS is no longer discernible by any invasive imaging method and endothelial function is restored. Late luminal enlargement persists up to five years of follow-up without adaptive vessel remodelling.

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Introduction

Permanent metallic stents embedded in a coronary artery could preclude coronary revascularisation options, jail side branches, impair (long-term) endothelial function, impair non-invasive imaging and, most importantly, are associated with late and very late stent thrombosis[1]. Conceptually, a bioresorbable scaffold could help overcome these long-term pitfalls of metallic scaffolds.

The first-generation everolimus-eluting bioresorbable vascular scaffold (Absorb BVS; Abbott Vascular, Santa Clara, CA, USA) demonstrated safety and efficacy in 30 patients included in the BVS cohort A study[1]. At angiographic follow-up, the luminal late loss was 0.43±0.37 mm at six months and 0.48±0.28 mm at two years[1,2]. Intravascular ultrasound (IVUS) analysis revealed a decrease in scaffold area in the first six months together with low neointimal hyperplasia resulting in an overall reduction of 16.8% of the luminal area[3]. Interestingly, both IVUS and optical coherence tomography (OCT) showed a luminal area enlargement between six months and two years due to a reduction in plaque size without change in vessel size[2]. One third of the scaffold struts could not be visualised by OCT at two years. Moreover, there was an optically homogeneous vessel wall structure suggesting healing of the coronary artery[2].

Until now, the long-term scaffold biodegradation and vascular response following BVS implantation has not been systematically evaluated in human subjects. We aimed to assess the long-term vascular response of the first-generation everolimus-eluting BVS by multiple invasive imaging modalities, including IVUS, IVUS virtual histology (IVUS-VH), OCT and vasomotion testing.

Methods

PATIENT POPULATION

The design of the ABSORB cohort A study has already been published[1]. For the present study, we included patients from the Thoraxcenter Rotterdam cohort of the ABSORB cohort A study (n=16). All living patients (n=14; two patients died from a non-cardiac cause at 706 and 808 days post procedure, one from duodenal perforation and one from Hodgkin's disease) were asked to participate in this study. Eight out of 16 patients of the Rotterdam cohort of the ABSORB A trial provided written informed consent and underwent catheterisation and scaffold assessment with multiple imaging modalities between March 8 and July 20, 2012 **(Figure 1)**.

The long-term single-centre follow-up imaging data (quantitative coronary angiography, vasomotion test, greyscale intravascular ultrasound, virtual histology) were analysed by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) and compared to previous core laboratory data-on-file from the ABSORB cohort A study. OCT image analysis was performed by an independent researcher in the Erasmus Medical Center (AK).

STUDY PROCEDURES

The definitions of individual parameters have already been described in a prior manuscript[2]. The clinical endpoints included cardiac death, myocardial infarction, stent thrombosis and ischaemia-driven target lesion revascularisation according to the definitions

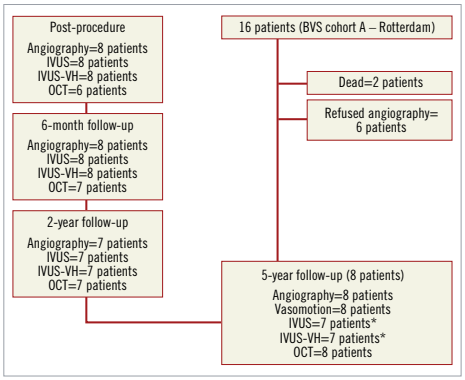

Figure 1. *Flow chart showing the patients included in the five-year follow-up study. *IVUS data could not be acquired for one the included patients at five-year follow-up.*

from the Academic Research Consortium[4]. Endothelium-dependent and endothelium-independent coronary vasomotion were studied using standard protocols[5]. Endothelial dysfunction was defined as vasoconstriction of >3% in mean vessel diameter between baseline and maximum dose acetylcholine (Ach).

IVUS acquisitions were performed using an Eagle Eye® catheter (Volcano Corp., Rancho Cordova, CA, USA) with automated continuous pullback at 0.5 mm/sec. IVUS-VH utilises backscattering of radiofrequency signals to provide information about tissue composition of the vessel wall. Four different plaque compositions, i.e., fibro-fatty, fibrous tissue, dense calcium and necrotic core were assessed on each cross-section and expressed as percentage (with each area totalling 100%). The polymeric scaffold struts were detected as dense calcified areas surrounded by necrotic core due to the strong backscattering properties of the polymer. The changes of these areas between implantation and follow-up were used as a surrogate marker to assess the polymer bioabsorption process. The methodology of OCT image acquisition for the baseline, six-month and two-year follow-up, using a first-generation OCT system with occlusive technique, has been previously described[1,2]. At five-year follow-up, all eight subjects underwent second-generation, non-occlusive OCT imaging using the commercially available C7 XR imaging console and the Dragonfly™ intravascular imaging catheter (both St. Jude Medical, St. Paul, MN, USA). Image acquisition has been previously described[6].

Scaffolds were assessed for the presence of incomplete apposition, intra-scaffold dissection and irregular lumen shape. Incomplete strut apposition was defined as the complete separation between strut and vessel wall with a distance larger than the strut thickness. Scaffolds with at least one incompletely apposed strut were considered incompletely apposed. Incompletely apposed struts located in front of side branch ostia, were considered side branch-related

struts and analysed separately. The number of side branches per scaffold with side branch-related incomplete strut apposition was recorded. Irregular lumen shape was defined as the presence of multiple intimal protrusions. Plaque morphology in each frame at five years was characterised, according to definitions used for native atherosclerosis, as fibrous, fibrocalcific and fibroatheromatous[6]. In the case of fibroatheromas, fibrous cap thickness was assessed and fibroatheromas with cap thickness <65 µm were classified as thin-cap fibroatheromas[7].

STATISTICAL ANALYSIS

This study was designed to provide preliminary observations and generate hypotheses for future studies. Baseline and procedural variables are presented as mean (±standard deviation [SD]) for continuous variables and as percentages for categorical variables. Paired comparisons of measurements performed after the procedure and in the different follow-up intervals were done by a Wilcoxon's signed rank test. No statistical adjustment was applied on the data set since no formal hypothesis testing was planned. The p-values represent exploratory analysis only and should therefore be interpreted with caution. All reported p-values are two-sided and regarded as statistically significant if ≤0.05. Statistical analysis was performed with SPSS for Windows version 15 (SPSS Inc., Chicago, IL, USA).

Results

The baseline characteristics of the population are shown in **Table 1**. At five years, there were no cardiac deaths, stent thromboses or myocardial infarctions, and only one patient had a target vessel revascularisation (TVR) at 106 days and 1,780 days and a target lesion revascularisation (TLR) at 2,218 days. At 106 days, the patient underwent catheterisation due to persistent chest pain. The Absorb BVS in the distal circumflex coronary artery was patent; however, the proximal circumflex coronary artery showed a narrowing with occlusive spasm on further testing with methergine. A paclitaxel-eluting stent was placed in the proximal circumflex coronary which was 7 mm from the proximal edge of the Absorb BVS. At 1,780 days, the patient had a repeat angiography for recurrence of stable angina. This time an everolimus-eluting stent was used to treat a significant *de novo* lesion in the intermediate branch. At 2,218 days, the angiographic follow-up performed because of this study showed a significant lesion distal of the Absorb BVS scaffold with a fractional flow reserve of 0.79. This lesion was located within 5 mm of the distal marker of the Absorb BVS and treated with a Tryton bifurcation stent (Tryton Medical, Inc., Durham, NC, USA) and an everolimus-eluting stent.

Table 1. Baseline and procedural characteristics.

Number of patients (n=8)		BVS
Demographic characteristics	Age, years (±SD)	65.1 (±8.6)
	Male, %	75 (6/8)
Cardiac history (%)	Prior target vessel intervention	12.5 (1/8)
	Prior myocardial infarction	12.5 (1/8)
Risk factors (%)	Current smoking	12.5 (1/8)
	Hypertension	50 (4/8)
	Hypercholesterolaemia	37.5 (3/8)
	Diabetes	12.5 (1/8)
Treated vessel (%)	RCA	12.5 (1/8)
	LAD	37.5 (3/8)
	LCX	50.0 (4/8)
ACC lesion type (%)	A	0 (0/8)
	B1	50 (4/8)
	B2	50 (4/8)
	C	0 (0/8)
QCA	Mean reference vessel diameter, mm (±SD)	3.0 (±0.6)
	Minimum luminal diameter, mm (±SD)	1.1 (±0.3)
	Diameter stenosis, % (±SD)	64.6 (±10.7)
	Lesion length, mm (±SD)	10.8 (±4.0)

Data are presented as percentages or means (±SD). SD: standard deviation; RCA: right coronary artery; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery.

At five-year angiography, there was no evidence of significant stenosis in the coronary artery segments scaffolded by the Absorb BVS as identified by the proximal and distal radiopaque markers. All patients showed an increase in minimum luminal diameter (MLD) compared to the previous invasive follow-up at two years (except for one patient who did not have angiographic follow-up at two years). The patient-level data regarding MLD are depicted in **Table 2**. Overall, there was a trend towards an increase in MLD at five years (2.14±0.38 mm) compared to two years (1.95±0.37 mm; p=0.09), resulting in a decrease in late loss (0.22±0.34 mm vs. 0.39±0.31 mm; p=0.09; respectively).

Table 2. Quantitative coronary angiography.

Quantitative coronary angiography	Before procedure	After procedure	6 months	2 years	5 years	*p*-value after procedure vs. 5 years	*p*-value 6 months vs. 5 years	*p*-value 2 years vs. 5 years
N	8	8	8	7	8			
Reference vessel diameter (mm)	3.02 (±0.56)	3.04 (±0.20)	2.93 (±0.21)	2.78 (±0.08)	2.83 (±0.30)	0.02	0.67	0.74
In-scaffold minimum luminal diameter (mm)	1.06 (±0.30)	2.36 (±0.30)	2.10 (±0.31)	1.95 (±0.37)	2.14 (±0.38)	0.09	0.67	0.09
In-scaffold diameter stenosis (%)	64.56 (±10.66)	22.33 (±6.68)	28.19 (±10.99)	29.93 (±13.26)	24.67 (±9.77)	0.21	0.50	0.07
In-scaffold late loss (mm)	–	–	0.26 (±0.25)	0.39 (±0.31)	0.22 (±0.34)	–	0.67	0.09

In keeping with the angiographic findings, IVUS data showed a trend towards an increase in mean lumen area at five years (6.96±1.13 mm^2) compared to six months (6.17±0.74 mm^2; p=0.06) and two years (6.56±1.16 mm^2; p=0.12) **(Table 3)**. This was primarily due to a persistent reduction in plaque size between six months and five years (9.17±1.86 mm^2 vs. 7.57±1.63 mm^2; p=0.03), resulting in an increased lumen area with no evidence of vessel dilatation/ectasia. Dense calcium area and necrotic core area were significantly reduced at five years when compared to baseline **(Table 3)**. The dense calcium area significantly decreased from 1.32±0.75 mm^2 to 0.52±0.51 mm^2 (p=0.03), whereas the necrotic core area decreased from 1.79±0.80 mm^2 to 0.74±0.66 mm^2 (p=0.03). The greatest reduction in these components occurred within two years after Absorb BVS implantation. No changes in plaque composition were observed between two and five years.

At five-year follow-up, mean and minimum luminal area by OCT were significantly increased compared to the six-month and the two-year follow-up, while there was no significant difference from baseline measurements immediately after the index procedure **(Figure 2, Table 4)**. No scaffold struts could be identified by OCT at five years, providing evidence of a continued and completed resorption process from the second year on. Morphological assessment is represented in **Table 4**. Multiple luminal protrusions which caused a corrugated ring appearance in all patients at six months were no longer evident in any patient by five years. All baseline intra-scaffold dissections (n=5) were healed by five years. Two patients showed a focally irregular lumen contour, one of whom had a short intimal dissection, not present at earlier investigations, at the overlap between the BVS and a metallic stent implanted at baseline as a bail-out procedure. There was no incomplete scaffold apposition in any case, as scaffold struts could not be detected. Side branch-related incomplete scaffold apposition was identified in seven out of eight scaffolds at previous follow-ups, while, at the five-year follow-up of the same patients, tissue bridges/neocarina **(Figure 3)** were evident at the site of previously detected side branch-related struts.

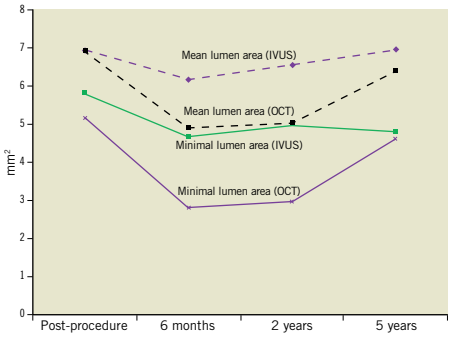

Figure 2. *Mean and minimum luminal area of IVUS and OCT analysis.*

Endothelium-dependent vasomotion was present in the proximal and distal scaffold coronary segment as the mean lumen diameter decreased by 3.2% (from 2.53 mm to 2.45 mm) and 5.2% (from 2.49 mm to 2.36 mm), respectively, after maximum dose Ach compared to baseline angiography. Endothelium-independent vasomotion was not observed in the proximal or distal segment. Neither endothelium-dependent nor endothelium-independent vasomotion was observed in the scaffolded coronary segment, due to a heterogeneous response of four patients showing vasoconstriction and four patients showing vasodilatation on maximum dose Ach. A detailed individual response is depicted in **Figure 4**.

Table 3. Intravascular ultrasound and intravascular ultrasound virtual histology.

	After procedure	6 months	2 years	5 years	*p*-value after procedure vs. 5 years	*p*-value 6 months vs. 5 years	*p*-value 2 years vs. 5 years
N	8	8	7	7			
Greyscale IVUS							
Vessel area (mm^2)	15.72 (±3.00)	15.34 (±2.00)	14.09 (±1.66)	14.52 (±1.81)	0.60	0.40	0.75
Average lumen area (mm^2)	6.95 (±0.63)	6.17 (±0.74)	6.56 (±1.16)	6.96 (±1.13)	0.75	0.06	0.12
Plaque area (mm^2)	8.78 (±2.83)	9.17 (±1.86)	7.54 (±1.24)	7.57 (±1.63)	0.60	0.03	0.92
Minimum lumen area (mm^2)	5.81 (±0.62)	4.67 (±0.77)	4.96 (±1.08)	4.81 (±2.04)	0.60	0.74	0.75
IVUS-VH							
Dense calcium (%)	23.31 (±8.40)	18.85 (±7.59)	15.43 (±6.89)	14.40 (±6.18)	0.03	0.40	0.46
Dense calcium area (mm^2)	1.32 (±0.75)	1.01 (±0.40)	0.55 (±0.31)	0.52 (±0.51)	0.03	0.09	0.12
Fibro-fatty (%)	5.31 (±3.28)	6.33 (±4.15)	8.05 (±5.86)	10.43 (±3.19)	0.03	0.13	0.25
Fibro-fatty area (mm^2)	0.34 (±0.28)	0.36 (±0.30)	0.28 (±0.25)	0.35 (±0.23)	0.92	0.31	0.75
Fibrous (%)	41.00 (±8.50)	51.50 (±8.85)	51.06 (±9.00)	55.31 (±9.55)	0.03	0.50	0.25
Fibrous area (mm^2)	2.48 (±1.22)	2.94 (±1.31)	1.77 (±0.47)	1.85 (±1.05)	0.60	0.06	0.92
Necrotic core (%)	30.38 (±4.71)	23.32 (±8.23)	25.46 (±9.37)	19.86 (±6.62)	0.03	0.40	0.17
Necrotic core area (mm^2)	1.79 (±0.80)	1.29 (±0.74)	0.90 (±0.43)	0.74 (±0.66)	0.03	0.18	0.03

Table 4. Quantitative and qualitative OCT findings.

Table measurements	After procedure	6 months	2 years	5 years	*p*-value after procedure vs. 5 years	*p*-value 6 months vs. 5 years	*p*-value 2 years vs. 5 years
N	6	7	7	8			
Minimal lumen area, mm²	5.16±0.74	2.81±1.57	2.97±1.26	4.62±1.44	0.60	0.02	0.02
Mean lumen area, mm²	6.91±0.88	4.89±1.29	5.03±1.24	6.39±1.18	0.46	0.03	0.02

Table patient level	Incomplete scaffold apposition			Side branches with side branch struts or tissue bridges (n)				Intra-scaffold dissection				Irregular lumen shape			Plaque characterisation*
Months since implantation	0	6	24	0	6	24	60	0	6	24	60	6	24	60	60
Patient 1	–	–	–	1	1	1	1	+	–	–	–	+	–	–	Fibroatheroma/fibrous
Patient 2	N/A	–	–	N/A	3	3	3	N/A	+	–	–	+	–	–	Fibrous/fibroatheroma/ fibrocalcific
Patient 3	–	–	–	2	2	2	1	+	–	–	–	+	–	–	Fibrous/fibroatheroma
Patient 4	+	+	–	1	1	1	1	–	–	–	–	+	–	–	Thin-cap fibroatheroma/ fibrous
Patient 5	–	–	N/A	2	2	N/A	2	–	–	N/A	–	+	N/A	–	Fibrocalcific/fibroatheroma
Patient 6	–	–	–	2	2	2	2	+	+	–	–	+	+	–	Fibrous/fibroatheroma
Patient 7	–	–	–	0	0	0	0	+	+	–	–	+	+	–	Fibrous
Patient 8	N/A	N/A	–	N/A	N/A	3	3	N/A	N/A	–	–	N/A	–	–	Fibrous/fibrocalcific/ fibroatheroma

Data are presented as mm² (±SD). The table consists of quantitative (top) and individual qualitative OCT findings (beneath) at different follow-up intervals. +positive; -: negative; N/A: not available

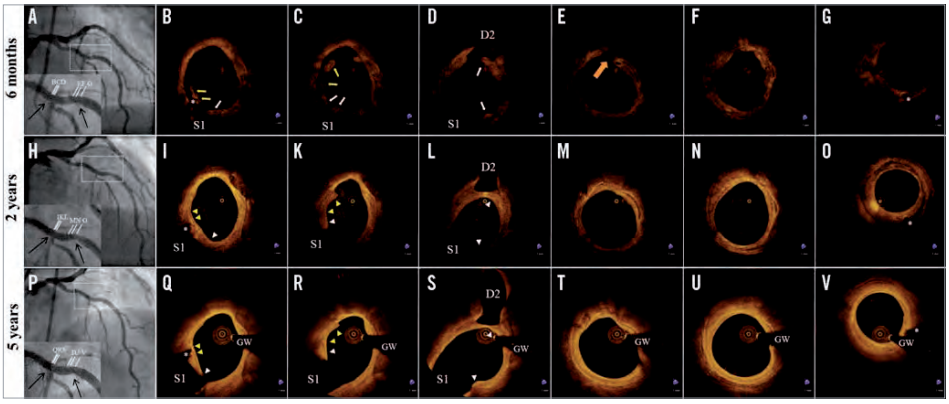

Figure 3. *Serial assessment of scaffold-vascular wall interaction by optical coherence tomography (OCT) in patient 2. A) Coronary angiography six months after BVS implantation at the mid left anterior descending artery. Arrows indicate position of the radiopaque markers at the extremities of the scaffold. B-G) OCT assessment six months after BVS implantation. Incompletely apposed struts (yellow arrows) and side branch-related struts (white arrows) in front of diagonal and septal branches were visualised. Intra-scaffold dissection (orange arrow) and irregular lumen shape can be identified in panels E and F, respectively. H) Coronary angiography 24 months after BVS implantation. I-O) OCT assessment 24 months after BVS implantation. Previously incompletely apposed struts (yellow arrowheads) were integrated into the vessel wall (panels I-K), while side branch-related struts (white arrowheads) were connected by neointimal tissue bridges (panels I-L). Healing of the intra-scaffold dissection and recovery of regular lumen shape. P) Coronary angiography 74 months after BVS implantation. Q-V) OCT assessment 74 months after BVS implantation. Complete disappearance of the struts from the vascular wall and replacement by a signal-rich intimal layer that is separating the underlying plaque (fibrocalcific plaque - fibroatheroma) from the lumen. Note also the complete biodegradation of side branch-related struts and the thinning of tissue bridges. Asterisks indicate stent markers, GW indicates guidewire artefact, S1 indicates ostium of the septal branch and D2 of the diagonal branch.*

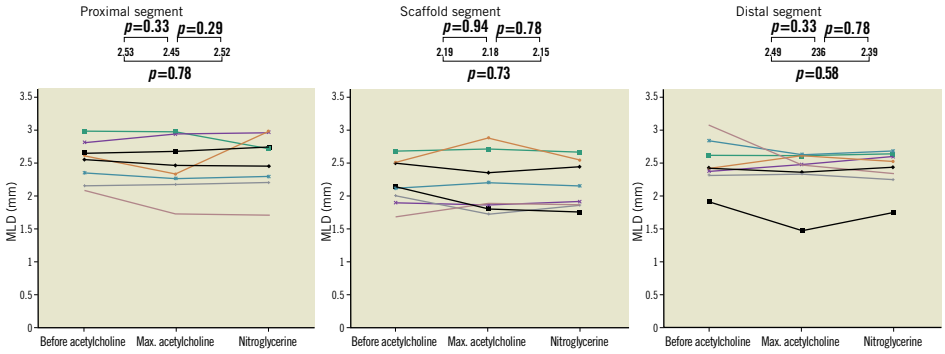

Figure 4. *Vasomotion testing. In these graphs you can see the individual changes of the patients in the proximal coronary segment, scaffold segment and distal segment. At the top, the MLD with the p-values are presented.*

Discussion

The main findings of the current study are the following. 1) The bioresorption process of the Absorb BVS has been completed, as no scaffold struts could be identified by OCT and dense calcium area and necrotic core area by IVUS-VH were significantly reduced at five years compared to baseline. 2) As suggested by OCT analysis, there is no evidence of incompletely apposed struts or struts jailing side branch ostia, and all baseline dissections were healed. 3) There was a trend towards an increase in mean and minimum lumen area at five years compared to two years as assessed by angiography and IVUS, while a significant increase was observed by OCT. The increase was primarily due to a persistent reduction in plaque area up to five years with no evidence of a change in vessel size. 4) The scaffolded coronary segments did not show signs of endothelial dysfunction, whereas a heterogeneous response of the scaffolded coronary segments was observed in response to vasoactive agents. Overall, neither endothelium-dependent nor endothelium-independent vasomotion could be observed in the scaffolded coronary segment.

In the current study, four different intravascular imaging modalities demonstrated consistently that the bioresorption process of the first-generation Absorb BVS has been fully completed. There is a remarkable persistent late luminal enlargement and a reduction in plaque area without outward vessel remodelling up to five years after the first-generation Absorb BVS implantation. Recently, positive long-term findings were also reported for the non-drug-eluting fully biodegradable self-expanding Igaki-Tamai stent (Kyoto Medical Planning Co., Ltd., Kyoto, Japan; formerly, Igaki Medical Planning Co., Ltd.)[8]. In a limited cohort of 50 patients, the struts mostly disappeared within three years after implantation as assessed by IVUS data, although no other imaging modalities with higher sensitivity for detecting scaffold struts were utilised. In that study, the overall major adverse cardiac events rate was acceptable with a target lesion revascularisation rate of 28% at 10 years[8]. In our small cohort, there were no target lesion revascularisations performed in patients treated with the first-generation Absorb BVS at five-year follow-up (only one patient had a TLR at 2,218 days). This beneficial efficacy outcome of the Absorb BVS could have been caused by differences in scaffold design (such as balloon-expanding, drug-eluting, thinner strut thickness and less maximum circular unsupported scaffold area), but also due to intrinsic differences between the two scaffolds. Knowledge of the specific timeline and completion of the bioresorption process of the Absorb BVS in human coronary arteries is very important, as the scaffold should ideally provide uniform radial support for a certain period and afterwards preferably be fully bioresorbed to restore natural physiologic vasomotor function. The Absorb BVS characteristics come closer to achieving this ideal equilibrium, which may have contributed to this favourable efficacy outcome of our patient population.

Our previous published reports with a multi-imaging approach have shown that the bioresorption process of the Absorb BVS was still ongoing at two-year follow-up, as two thirds of the struts were still visible by OCT[2]. Our group recently reported that only one sixth of the struts were recognisable at four years by OCT in a porcine model[9]. In the current study, none of the struts was discernible by OCT at five years, suggesting a faster resorption process in human coronary arteries compared to porcine coronary arteries. Analysis of virtual histology data corroborates this finding, as the dense calcium area and necrotic core area, which can be used as a surrogate marker of the bioresorption process of polymeric struts, were significantly reduced at five years compared to baseline.

IVUS data showed a tendency towards an increase in mean lumen area at five years compared to six months and two years, primarily due to a persistent reduction in plaque area up to five years. A relative reduction in plaque area of 14% in five years achieved by this

local treatment has not been observed before. Therefore, it could even have better plaque-reducing capabilities than (high-intensity) statin treatment, which showed only a reduction of roughly 1% in percentage atheroma volume at two years[10]. Although all patients were on statin treatment, this observed major decrease in plaque area size is an interesting finding that needs further research.

The OCT findings are consistent with a favourable healing response and the absence of device-induced vascular wall toxicity. This is of importance as first-generation drug-eluting stents have been associated with an impaired healing response and vascular toxicity, factors contributing to very late stent thrombosis[11]. Furthermore, metallic platforms have been associated with the development of neoatherosclerosis, which can also contribute to very late stent thrombosis, reported to occur even 15 years following stent implantation[12]. In our patients, OCT revealed the complete disappearance of scaffold struts. We assume, based on the vast evidence in the literature, that this vascular reaction is favourable and potentially reduces the risk of very late stent thrombosis. We further speculate that the observed development of a homogeneous tissue layer over the underlying plaque together with the possibility of observed everolimus-induced autophagy of the macrophages could reduce the risk of new thrombotic events caused by plaque progression[13].

The previous two-year report observed the presence of a functionally active endothelium at the site of the scaffold implantation[2]. In fact, five out of nine patients tested showed vasodilatation with intracoronary acetylcholine. In the present study, four out of eight patients had a more than 3% increase in vessel size after maximum dose of acetylcholine. Two other patients had a less than 3% response, while two patients had more than 3% vasoconstriction (3.9%). These findings are consistent with restoration and preservation of vasomotor function in the scaffolded segment, a desirable effect observed in the absence of a rigid structure.

This study provides evidence for the first time that the beneficial effects of the bioresorbable scaffold are sustained five years after implantation, and of an ongoing lumen enlargement from two years to five years with concomitant reduction in plaque area. Further clinical evidence from ongoing BVS studies can corroborate the current hypothesis and provide a role for BVS in the treatment of coronary artery disease. Furthermore, in the light of the findings of the PROSPECT study, which concluded that specific morphological characteristics of non-culprit lesions in patients with acute coronary syndrome are associated with future events, a device with a favourable safety profile that can shield the lumen from the underlying plaque by a protective homogeneous layer without causing any luminal compromise in the long term could conceptually be used in the setting of high-risk non-stenotic lesions in the future[14].

Limitations

The current study had some limitations. It included a small number of patients and therefore the various parameters that were investigated should be considered as exploratory. Moreover, not all patients who were invited participated in this study. Whether our findings are representative of the whole cohort remains questionable. However, baseline clinical and angiographic characteristics were not different from the entire ABSORB cohort A which can be expected to behave similarly. Third, OCT was performed using a second-generation system with a non-occlusive technique, whereas previous OCT examinations were performed with a first-generation system with proximal balloon occlusion. Although second-generation OCT is associated with a better imaging quality and high reproducibility, it might have slightly overestimated luminal measurements.

Conclusions

In conclusion, the observations made in the current study suggest a highly beneficial clinical and invasive imaging outcome at long-term follow-up. In this series of patients, there was evidence of small but consistent late lumen enlargement at five years, primarily caused by a reduction of the plaque area. The complete bioresorption of the scaffold without signs of endothelial dysfunction suggests the recovery of a functional vascular wall and the elimination of a substrate for late stent complications. All these beneficial findings need to be confirmed in larger studies.

Impact on daily practice

This is the first study describing the five-year results of several imaging modalities of patients treated with first-generation bioabsorbable vascular scaffolds. The results indicate that the bioabsorption process has been fully completed with a late luminal enlargement up to five years of follow-up without signs of adaptive vessel remodelling. The increase in luminal enlargement is due to an impressive reduction in plaque area of 14% in five years, which has not been observed before. These encouraging long-term results of the first-generation bioabsorbable vascular scaffolds will pave the way for larger randomised controlled trials in the future.

Guest Editor

This paper was Guest Edited by Manel Sabaté, MD, PhD, Servicio de Cardiología, Clínic Hospital, Barcelona, Spain.

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Conflict of interest statement

R.J. van Geuns has received a speaker's fee and served on the European advisory board of Abbott Vascular. Y. Onuma has received a speaker's fee from Abbott Vascular. The other authors have no conflicts of interest to declare. The Guest Editor has no conflicts of interest to declare.

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Part IV

PERCUTANEOUS CORONARY INTERVENTIONS WITH UNDERLYING METABOLIC DISORDERS

4.1

Long-term outcome of the unrestricted use of everolimus-eluting stents compared to sirolimus-eluting stents and paclitaxel-eluting stents in diabetic patients: The Bern-Rotterdam diabetes cohort study.

Simsek C, Räber L, Magro M, Boersma E, Onuma Y, Stefanini GG, Zanchin T, Kalesan B, Wenaweser P, Jüni P, van Geuns RJ, van Domburg RT, Windecker S, Serruys PW

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Long-term outcome of the unrestricted use of everolimus-eluting stents compared to sirolimus-eluting stents and paclitaxel-eluting stents in diabetic patients: The Bern–Rotterdam diabetes cohort study

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ABSTRACT

Background: Newer generation everolimus-eluting stents (EES) improve clinical outcome compared to early generation sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES). We investigated whether the advantage in safety and efficacy also holds among the high-risk population of diabetic patients during long-term follow-up.

Methods: Between 2002 and 2009, a total of 1963 consecutive diabetic patients treated with the unrestricted use of EES (n = 804), SES (n = 612) and PES (n = 547) were followed throughout three years for the occurrence of cardiac events at two academic institutions. The primary end point was the occurrence of definite stent thrombosis.

Results: The primary outcome occurred in 1.0% of EES, 3.7% of SES and 3.8% of PES treated patients ([EES vs. SES] adjusted HR = 0.58, 95% CI 0.39–0.88; [EES vs. PES] adjusted HR = 0.29, 95% CI 0.13–0.67). Similarly, patients treated with EES had a lower risk of target-lesion revascularization (TLR) compared to patients treated with SES and PES ([EES vs. SES], 5.6% vs. 11.5%, adjusted HR = 0.68, 95% CI: 0.55–0.83; [EES vs. PES], 5.6% vs. 11.3%, adjusted HR = 0.51, 95% CI: 0.33–0.77). There were no differences in other safety end points, such as all-cause mortality, cardiac mortality, myocardial infarction (MI) and MACE.

Conclusion: In diabetic patients, the unrestricted use of EES appears to be associated with improved outcomes, specifically a significant decrease in the need for TLR and ST compared to early generation SES and PES throughout 3-year follow-up.

1. Introduction

Diabetes mellitus (DM) has rapidly grown into a public health problem in the Western world [1]. Currently, a quarter of the patients undergoing percutaneous coronary intervention (PCI) have DM, which has been associated with higher restenosis and major adverse cardiac event (MACE) rates post-PCI compared to patients without DM [2–4]. Endothelial dysfunction, excessive platelet deposition and the over-expression of several growth factors, such as insulin-like growth factor-1, basic fibroblast growth factor and transforming growth factor-beta are some of the factors contributing to the increased MACE rates [5].

To date, several studies evaluated clinical outcome of the use of bare-metal stents (BMS) and early generation drug-eluting stents (DES) in patients with DM [6–8]. These randomized studies, demonstrated that sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) reduced both angiographic and clinical parameters of restenosis compared to BMS in diabetic patients with no significant difference in the rates of stent thrombosis [6–8]. Nonetheless, in a real-world setting, the benefit of SES and PES over BMS seems to be confined to only non-insulin-dependent diabetic patients [9].

Newer generation everolimus-eluting stents (EES) have thinner struts, thinner polymer coating and improved biocompatibility of the polymer layer compared to the early generation DES, theoretically reducing the risk of in-stent restenosis and thrombosis [10]. A recent pooled analysis of 4 randomized trials showed that EES significantly reduced the 2-year risk of mortality, stent thrombosis, myocardial

Abbreviations: aHR, Adjusted Hazard Ratio; ARC, Academic Research Consortium; BMS, Bare-Metal Stents; CI, Confidence Interval; DES, Drug-Eluting Stents; DM, Diabetes Mellitus; ECG, ElectroCardioGraphy; EES, Everolimus-Eluting Stents; IQR, Inter Quartile Range; MACE, Major Adverse Cardiac Events; MI, Myocardial Infarction; PCI, Percutaneous Coronary Intervention; PES, Paclitaxel-Eluting Stents; RESEARCH, Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital; SD, Standard Deviation; SES, Sirolimus-Eluting Stents; ST, Stent Thrombosis; TLR, Target-Lesion Revascularization; TVR, Target-Vessel Revascularization; T-SEARCH, Taxus–Stent Evaluated At Rotterdam Cardiology Hospital; X-SEARCH, XIENCE-Stent Evaluated At Rotterdam Cardiology Hospital.

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infarction and target-lesion revascularization compared to paclitaxel-eluting stents (PES) in patients without DM [11]. However, the advantage of everolimus-eluting stents over paclitaxel-eluting stents was not reproduced in the general diabetic population [11]. Similar non-significant findings in short-term clinical efficacy and safety parameters were shown between EES and SES in diabetic patients [12].

To date, it remains unclear whether there is any long-term clinical benefit associated with the implantation of EES compared to SES and PES in a large "all-comer" diabetic population. Therefore, we investigated the 3-year safety and efficacy profile of the unrestricted use of SES, PES and EES in diabetic patients of the Bern–Rotterdam study.

2. Methods

2.1. Patient population and study design

Between April 2002 and December 2009, a total of 12,945 consecutive "all-comer" PCI patients were treated at two academic centers in the Netherlands and Switzerland. All treated patients were included in the analysis without any restrictions to include a patient population representing the "real world". However, patients forming part of a randomized trial, which required protocol mandated angiographic follow-up, were excluded from the analysis because of the fact that it is a well-known trigger for coronary revascularization (n = 158). Additionally, patients receiving multiple stent types during the initial procedure were excluded from analysis (n = 606). The study population consisted of 1963 diabetic patients (16.1%), of which 804 patients were treated with EES (XIENCE V™, Abbott Vascular, Santa Clara, CA, or PROMUS™, Boston Scientific, Natick, MA, USA), 612 patients with SES (Cypher™, Cordis Corporation, Johnson and Johnson, Warren, NJ, USA) and 547 patients with PES (Taxus™, Express2™ or Liberté™, Boston Scientific, Natick, MA, USA) (Fig. 1). A total of 1100 patients (56.0%) were included in Rotterdam and 863 patients (43.0%) in Bern (Fig. 3). Since March 2007, EES has been the default strategy in the Thoraxcenter Rotterdam as part of the XIENCE Stent Evaluated At Rotterdam Cardiology Hospital (X-SEARCH) registry [10]. The Bern University Hospital has used EES since November 2006 on a daily alternating basis with biolimus-eluting stents and zotarolimus-eluting stents. The design of the study has been described previously [13].

The procedures were performed according to standard clinical guidelines and every patient was pre-treated with a loading dose of ≥300 mg clopidogrel and lifelong aspirin. No other thienopyridine or platelet aggregation inhibitor, besides aspirin and clopidogrel, was used during the study period. At the Thoraxcenter, Rotterdam, SES-patients were prescribed clopidogrel for a duration of at least 3 months unless one of the following criteria was present: multiple SES-implantation (≥stents), total stent length 36 mm or longer, chronic total occlusions and bifurcations, in which case the DAPT were prescribed for a longer period. DAPT were prescribed for at least 6 months for PES-patients and 12 months for EES-patients. At Bern University Hospital, all patients received clopidogrel for at least 12 months irrespective of stent type. The usage of glycoprotein IIb/IIIa inhibitors was left at the discretion of the interventional cardiologist.

2.2. Data collection and follow-up

Survival data for all patients were obtained from municipal civil registries on a yearly basis. All living patients received yearly a health-related postal questionnaire, consisting of queries regarding rehospitalisation and MACE. In Bern, patients who had undergone implantation of SES or PES had their last follow-up took place beginning on February 1, 2007, and beginning on February 1, 2010, for patients with EES. In Rotterdam, the last follow-up took place on July 1, 2008, for PES-patients, on July 1, 2008, for SES-patients and on April 1, 2011, for EES-patients. In case of a patient-reported recurrent rehospitalisation, the discharge report was screened for a potential cardiac adverse event. Whenever patient indicated a repeat angiography, the angiography CDs were screened for the type of event by independent cardiologists. In addition, the hospital database of both hospitals were screened for repeat angiographies. The total number of reviewed angiograms was 396.

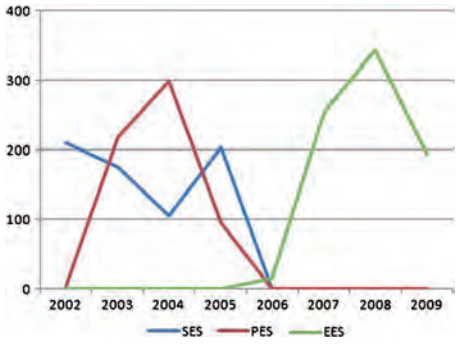

Fig. 1. The years (x-axis) and the number of stents used (y-axis) of the three stent types.

2.3. Definitions and end points

Diabetes was defined as the usage of an oral hypoglycemic agent or insulin. The predefined primary end point was the occurrence of definite stent thrombosis. Secondary safety end points included all-cause mortality, myocardial infarction (MI), the composite of cardiac death/MI, target-lesion revascularization (TLR) and MACE (defined as a composite of cardiac mortality, MI and TLR). MI was diagnosed by recurrent typical clinical symptoms and ischemic electrocardiography changes in combination with a CK-MB rise of three times the upper limit of normal or an elevation of more than two times the upper limit of normal in CK. TLR was defined as revascularization for a stenosis within the stent or within 5 mm proximal or distal to the stent. TVR was defined as a repeat PCI in the same vessel as the index procedure, in the presence of ischemic symptoms or positive functional ischemia study on the target vessel area and a significant minimal luminal diameter stenosis of at least 50%.

Stent thrombosis was defined according to the academic research consortium (ARC) criteria [14]. Stent thrombosis was categorized into early (within 30 days post-stent implantation), late (between 30 days and 1 year post-stent implantation) and very late (after 1 year post-stent implantation).

2.4. Statistical analysis

Baseline and procedural variables are presented as mean (±standard deviation (SD) for continuous variables and as percentages for categorical variables. The Pearson's chi square test was used to compare categorical variables and Student's *t*-test for continuous variables. The estimated cumulative incidence for the pre-specified end points was generated with the Kaplan–Meier method, and the difference between patients receiving SES, PES and EES was assessed with the log-rank test. Patients with multiple events were not censored during the follow-up period.

To adjust for baseline characteristics, a multivariate Cox proportional hazard regression model (95% confidence interval (CI)) was used. The total number of variables in the final Cox model was restricted according to generally accepted 10:1 events/degrees-of-freedom rule. The selection of variables entering the model was chosen a priori based on the literature. Additionally, a stepwise backward deletion of baseline variables was performed to add variables in the final model for each end point with a p-value ≤0.10. The following variables entered the multivariable Cox proportional hazards model: age, acute coronary syndrome, number of stents implanted, average stent diameter, prescription time of clopidogrel and type of stent (Table 3). An interaction term was added to the model to correct for potential heterogeneity between centers and used stent type. The proportional hazards assumption of the performed Cox multivariable analyses was assessed by the Schoenfeld partial residuals for all end points. The proportional hazards assumption was not violated for any of the end points. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All reported p-values are two-sided and regarded as statistically significant if ≤0.05. Statistical analysis was performed with SPSS for Windows version 15 (SPSS inc., Chicago, Illinois, USA).

3. Results

3.1. Population characteristics

The study population consisted of 1963 consecutive patients undergoing PCI with EES (n = 804), SES (n = 612) or PES (n = 547). A total of 1933 patients (98.3%) completed the last follow-up with 788 patients receiving EES (98.0%), 609 patients receiving SES (99.5%) and 536 patients receiving PES (98.0%). The median follow-up duration among patients treated with EES was 2.1 years (interquartile range (IQR): 1.4–2.8 years), 3.0 years (IQR: 2.0–3.0 years) for patients treated with SES and 2.4 years (IQR: 1.4–3.0 years) for patients treated with PES. Baseline and procedural characteristics stratified according to stent type are shown in Table 1. In summary, EES-patients were on average older, less frequently hypertensive, more often had a family cardiac history, more often treated with insulin, more often presented with a ST-elevation myocardial infarction, had a higher average stent diameter and were more often treated in the left main coronary artery or bypass graft compared to SES-patients and PES-patients. The duration of thienopyridine prescription post-stent implantation increased over time, being significantly longer in the EES-group than the SES-group

Table 1
Baseline and procedural characteristics stratified according to stent type.

Number of patients PES	EES	SES	PES	p-Value	
	(n = 804)	(n = 612)	(n = 547)	EES vs. SES	EES vs. PES
Demographic characteristics					
Age, years (±SD)	66.9 (±10.9)	64.1 (±10.5)	64.3 (±10.9)	<0.001	<0.001
Male (%)	70.0	70.4	67.3	0.9	0.3
Risk factors					
Current smoking (%)	29.9	39.9	26.5	<0.001	0.2
Hypertension (%)	66.0	74.7	71.1	<0.001	0.1
Hypercholesterolemia (%)	63.6	62.9	70.0	0.8	<0.05
Diabetes	–	–	–		
Insulin dependent (%)	28.7	24.0	20.3	<0.05	<0.001
Noninsulin dependent (%)	71.3	76.0	79.7	<0.05	<0.001
Family history (%)	33.3	26.6	29.8	<0.01	0.2
Renal impairment (%)	8.2	7.1	8.5	0.6	0.9
BMI, kg/m^2 (±SD)	28.9 (±5.0)	28.8 (±4.9)	28.6 (±4.4)	0.9	0.3
Clinical presentation					
Unstable angina/non-STEMI (%)	29.6	27.5	31.1	0.4	0.6
Acute coronary syndrome (%)	53.9	43.2	50.2	<0.001	0.2
ST-elevation MI (%)	24.0	15.7	18.9	<0.001	<0.05
Cardiogenic shock (%)	2.2	1.8	0.4	0.6	<0.01
LVEF[a] (±SD)	51.5 (±12.4)	53.9 (±12.4)	53.6 (±12.5)	<0.01	0.1
Disease severity					
Multi-vessel disease (%)	19.5	21.9	17.0	0.3	0.2
Bifurcation (%)	9.6	13.2	13.3	0.2	0.1
Number of stents (±SD)	2.0 (±1.2)	2.0 (±1.1)	2.2 (±1.3)	0.2	0.3
Number of lesions (±SD)	1.8 (±1.0)	1.5 (±0.7)	1.5 (±0.7)	<0.001	<0.001
Stent diameter, mm (±SD)	3.0 (±0.4)	2.8 (±0.3)	2.9 (±0.4)	<0.001	<0.01
Stent length, mm (±SD)	35.0 (±25.4)	35.9 (±23.7)	42.5 (±29.4)	0.8	<0.001
Treated vessel (%)					
RCA	34.8	31.3	35.6	0.2	0.8
LAD	48.1	51.7	48.6	0.2	0.9
LCX	27.2	29.6	28.2	0.3	0.7
LM	5.0	1.6	2.9	<0.001	0.1
Bypass graft	5.7	2.8	1.3	<0.01	<0.001
Medication					
Aspirin (%)	96.5	98.3	98.5	<0.05	<0.05
Clopidogrel (%)	97.7	99.0	98.5	0.3	0.1
Clopidogrel duration, months (±SD)	14.4 (±11.0)	9.7 (±11.2)	7.2 (±4.6)	<0.001	<0.001
GP IIb/IIIa inhibitor (%)	17.5	16.4	18.9	0.6	0.5
Betablocker (%)	50.4	62.0	64.6	<0.001	<0.001
ACE-inhibitor (%)	35.1	62.3	55.0	<0.001	<0.001
Calcium antagonist (%)	6.3	23.1	29.9	<0.01	<0.001
Statin (%)	84.5	78.1	80.2	<0.05	<0.05

Data are presented as percentages or means (±SD). SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; EES, everolimus-eluting stents; SD, standard deviation; BMI, body mass index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, Left main coronary artery.
[a] LVEF data is based on the Bern cohort.

and PES-group, respectively (14.4 months ± 11.0 vs. 9.7 months ± 11.2 vs. 7.2 months ± 4.6; p < 0.001).

3.2. 3-Year clinical outcome

At 3-year follow-up, the occurrence of definite stent thrombosis was significantly lower in the EES-group compared to the SES-group and PES-group (Tables 2 and 4, Fig. 2). The difference in favor of EES was mainly due to a lower risk of early ST (within the first 30 days after PCI) and a trend towards a lower risk of very late ST. In addition, EES-patients had a lower risk of TLR compared to patients treated with SES and PES The difference in rates of TLR between stent types occurred during the first year after PCI and was sustained until 3-year follow-up without evidence of diminished efficacy over time (Fig. 3).

Multivariate Cox regression analysis showed that no difference between stent types in terms of all-cause mortality, MI and MACE (the composite end point of cardiac death and/or MI), was significantly lower in EES-patients compared to PES-patients.

Patients treated with insulin had similar definite stent thrombosis rates compared to non-insulin dependent DM patients [adjusted HR = 0.74, 95% CI: 0.36–1.53]. Also, there were no differences in TLR [adjusted HR = 0.82, 95% CI: 0.56–1.21] and TVR rates [adjusted HR = 0.92, 95% CI: 0.68–1.23]. Insulin-dependent DM patients had higher all-cause mortality [adjusted HR = 1.51, 95% CI: 1.18–1.95] and cardiac mortality [adjusted HR = 1.67, 95% CI: 1.23–2.56] rates compared to those treated without insulin (Table 4).

In both insulin-dependent and non-insulin dependent DM patients, definite stent thrombosis rates were lower in patients treated with EES compared to those treated with SES and PES. However, it only reached statistical significance compared to PES-patients [adjusted HR = 0.39, 95% CI: 0.16–0.98] in the non-insulin dependent DM group. In addition, TLR rates of non-insulin dependent DM patients treated with EES were significantly lower compared to those treated with SES [adjusted HR = 0.61, 95% CI: 0.41–0.91], although this effect was attenuated in insulin-dependent DM-patients [adjusted HR = 0.72, 95% CI: 0.45–1.16].

4. Discussion

The main findings of this study show that in a “real world” diabetic population, implantation of new generation EES is associated with

Table 2
Crude event rates and multivariate analysis stratified according to different stent types at 3-years.

	EES (n = 804)	SES (n = 612)	PES (n = 547)	EES vs. SES	EES vs. PES
	Number of events (%)			Multivariate HR [95% CI]	
Mortality					
All-cause	122 (17.4%)	91 (12.9%)	76 (14.9%)	1.05 [0.91–1.21]	0.92 [0.69–1.24]
Non-cardiac	38 (5.4%)	32 (4.5%)	27 (5.3%)	1.07 [0.84-1.36]	0.87 [0.52–1.45]
Cardiac	84 (12.0%)	59 (8.4%)	49 (9.6%)	1.04 [0.88–1.23]	0.95 [0.66–1.37]
MI	22 (3.1%)	42 (5.7%)	37 (7.4%)	0.79 [0.60–1.06]	0.72 [0.34–1.54]
CD/MI	102 (14.0%)	97 (14.0%)	83 (16.7%)	0.81 [0.61–1.08]	0.43 [0.22–0.83]
ST					
Def/prob	52 (6.8%)	60 (8.7%)	53 (10.2%)	0.89 [0.74–1.08]	0.70 [0.48–1.03]
Definite	8 (1.0%)	23 (3.7%)	20 (3.8%)	0.58 [0.39–0.88]	0.29 [0.13–0.67]
Early	2 (0.2%)	11 (1.8%)	9 (1.7%)	0.40 [0.19–0.85]	0.15 [0.03–0.67]
Late	3 (0.4%)	3 (0.5%)	2 (0.4%)	0.88 [0.39–1.95]	0.97 [0.16–5.88]
Very late	3 (0.4%)	9 (1.4%)	9 (1.7%)	0.66 [0.34–1.29]	0.29 [0.08–1.08]
MACE	133 (18.0%)	144 (21.7%)	112 (20.6%)	0.96 [0.78–1.18]	0.77 [0.47–1.26]
Revascularization					
TVR	74 (10.3%)	107 (17.4%)	77 (16.8%)	0.74 [0.64–0.87]	0.62 [0.45–0.87]
TLR	41 (5.6%)	73 (11.5%)	51 (11.3%)	0.68 [0.55–0.83]	0.51 [0.33–0.77]
TLR*	27 (3.5%)	46 (7.2%)	34 (7%)	0.43 [0.26–0.70]	0.68 [0.53–0.87]
TLR**	14 (2.1%)	27 (4.3%)	17 (4.3%)	0.54 [0.26–1.12]	0.80 [0.53–1.20]

	IDDM (n = 489)					NIDDM (n = 1474)				
	EES (n = 231)	SES (n = 147)	PES (n = 111)	EES vs. SES	EES vs. PES	EES (n = 573)	SES (n = 465)	PES (n = 436)	EES vs. SES	EES vs. PES
	Number of events (%)			Multivariate HR [95% CI]		Number of events (%)			Multivariate HR [95% CI]	
Mortality										
All-cause	39 (23.0%)	26 (19.9%)	23 (25.7%)	1.13 [0.84–1.53]	0.85 [0.48–1.53]	83 (19.7%)	65 (15.3%)	53 (15.3%)	1.08 [0.84–1.40]	1.16 [0.77–1.74]
Non-cardiac	13 (10.1%)	5 (4.3%)	7 (8.5%)	4.56 [1.37–15.2]	1.12 [0.36–3.43]	58 (12.9%)	27 (7.0%)	20 (6.2%)	1.40 [0.82–2.39]	1.88 [0.78–4.57]
Cardiac	26 (14.3%)	21 (16.2%)	16 (18.7%)	0.96 [0.68–1.35]	0.77 [0.38–1.57]	25 (7.8%)	38 (8.9%)	33 (9.8%)	1.01 [0.74–1.39]	1.10 [0.68–1.78]
MI	4 (2.0%)	11 (10.2%)	6 (10.0%)	0.57 [0.27–1.18]	0.64 [0.07–5.67]	18 (5.1%)	31 (8.2%)	31 (8.7%)	0.89 [0.50–1.58]	0.90 [0.38–2.13]
CD/MI	30 (14.4%)	30 (23.8%)	22 (27.3%)	0.88 [0.65–1.19]	0.69 [0.37–1.29]	72 (16.8%)	67 (16.1%)	61 (17.1%)	0.96 [0.73–1.26]	0.88 [0.59–1.32]
ST										
Def/Prob	12 (7.3%)	15 (13.5%)	9 (14.7%)	0.95 [0.55–1.66]	0.80 [0.32–1.99]	40 (8.8%)	45 (10.9%)	44 (12.3%)	1.08 [0.80–1.43]	0.71 [0.45–1.10]
Definite	1 (0.5%)	6 (4.8%)	2 (4.3%)	0.35 [0.10–1.18]	0.37 [0.03–4.30]	7 (2.0%)	17 (4.3%)	18 (5.6%)	0.95 [0.54–1.69]	0.39 [0.16–0.98]
Early	0 (0%)	4 (2.7%)	0 (0%)	–	–	2 (0.4%)	7 (1.5%)	9 (2.1%)	0.74 [0.26–2.11]	0.19 [0.04–0.93]
Late	1 (0.5%)	0 (0%)	0 (0%)	–	–	2 (0.4%)	3 (0.7%)	2 (0.5%)	1.38 [0.35–5.43]	0.74 [0.10–5.44]
Very late	0 (0%)	2 (2.1%)	2 (4.3%)	–	–	3 (1.2%)	7 (2.1%)	7 (3.0%)	1.39 [0.56–3.47]	0.65 [0.15–2.74]
MACE	39 (22.6%)	37 (29.1%)	27 (33.8%)	0.90 [0.69–1.18]	0.75 [0.43–1.32]	94 (21.3%)	107 (25.2%)	85 (23.9%)	0.84[0.67–1.05]	0.68 [0.43–1.08]
Revascularization										
TVR	19 (12.8%)	24 (19.2%)	14 (19.4%)	0.75 [0.52–1.08]	0.66 [0.29–1.50]	55 (14.4%)	83 (20.7%)	63 (19.3%)	0.68 [0.50–0.93]	0.68 [0.45–1.03]
TLR	11 (8.3%)	14 (11.3%)	8 (13.2%)	0.72 [0.45–1.16]	0.78 [0.26–2.33]	30 (8.2%)	59 (14.4%)	43 (12.7%)	0.61 [0.41–0.91]	0.60 [0.35–1.02]
TLR*	7 (3.4%)	8 (5.6%)	4 (4.0%)	0.64 [0.34–1.20]	0.89 [0.16–5.06]	20 (3.8%)	38 (8.6%)	30 (7.4%)	0.63 [0.40–0.98]	0.55 [0.29–1.06]
TLR**	4 (5.1%)	6 (6.0%)	4 (9.4%)	0.82 [0.40–1.68]	0.71 [0.17–3.03]	10 (3.5%)	21 (6.4%)	13 (5.7%)	0.52 [0.20–1.34]	0.71 [0.28–1.82]

CD = cardiac death; CI = confidence interval; Def = definite; EES = everolimus-eluting stent; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin dependent diabetes mellitus; SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent; Prob = probable; HR = hazard ratio; MACE = Major Adverse Cardiac Events; MI = myocardial infarction; n.a. = not applicable; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization. TLR* shows the occurrence of TLR (%) in the period between 0 and 1 year. TLR** shows the occurrence of TLR (%) in the period between 1 and 3 years.

lower rates of definite stent thrombosis as compared to both SES and PES at 3-year follow-up. This difference emerged during the early period and showed a trend towards a lower risk during the very late period. Target lesion revascularization was performed less frequently in the EES group compared to the SES- and PES-group. The use of EES reduced the occurrence of TLR by 32% compared to SES and 49% compared to PES. The advantage in terms of efficacy is largely accrued during the first year following PCI with maintenance of superiority up to three years. There appears to be no differences in rates of ST and TLR between DM-patients on insulin treatment compared to those treated with oral medication. However, insulin-dependent diabetic patients had higher all-cause and cardiac mortality rates compared to non-insulin dependent diabetic patients. These results were consistent with the findings of our previous paper, where we showed that EES resulted in a lower rate of definite ST compared to SES [HR = 0.51, 95% CI: 0.34–0.77] and PES [HR = 0.34, 95% CI: 0.23–0.50] in patients without diabetes mellitus [15].

The clinical question of whether the safety and efficacy of EES are significantly better than SES and PES still needs to be addressed in

Table 3
Hazard ratio and 95% confidence interval for risk factors associated with definite stent thrombosis during the entire follow-up period from multivariable Cox regression analysis. The total number of variables entering the multivariable Cox proportional hazards model was restricted to 5 (according to the 10:1 events/degrees-of-freedom rule).

Variables	Hazard ratio	95% CI
Age	0.98	0.95–1.01
Acute coronary syndrome	3.47	1.62–7.43
Number of stents	1.36	1.11–1.67
Average stent diameter	0.43	0.16–1.18
Prescription time clopidogrel	0.94	0.86–1.02

patients with diabetes mellitus. These patients have worse clinical outcome when compared to the general population as previously shown in the pooled COMPARE and SPIRIT trials [11]. In this pooled analysis the advantage of EES over PES seen in the overall population failed to emerge in the diabetic population. Treatment with EES was associated with a reduction in TLR rates among non-insulin dependent DM patients, whereas a trend towards higher TLR rates was observed in insulin-dependent DM patients [11]. Moreover, an angiographic subgroup analysis of the SPIRIT-III trial showed that the differences in in-stent luminal late loss at 8-months between EES and PES (0.12 vs. 0.27 mm) were less pronounced in the diabetic population (0.18 vs. 0.24 mm) [16]. In our study, the implantation of EES was associated with lower ST and TLR rates compared to SES and PES in the insulin-dependent group, although it did not reach statistical significance. The antiproliferative potency of everolimus has been shown to be non-inferior to sirolimus, which is reflected in a similar in-stent lumen late loss in the general population (0.10 vs. 0.05 mm) [17]. Similarly, in the ESSENCE-DIABETES trial, angiographic in-stent late lumen loss was non-inferior among patients treated with EES compared to those treated with SES at 8-months (0.23 vs. 0.37 mm) [12]. In this non-inferiority trial, no significant difference was observed for clinical safety and efficacy end points.

Our study adds to the increasing evidence of lower risk of ST with newer generation DES [15,18,19]. We previously described that EES were associated with a lower risk of definite stent thrombosis compared with early generation drug-eluting stents in a "real-world" setting [15]. A finding was also reproduced in the diabetic population. These initial observations from crude sub-analysis were intriguing since no previous

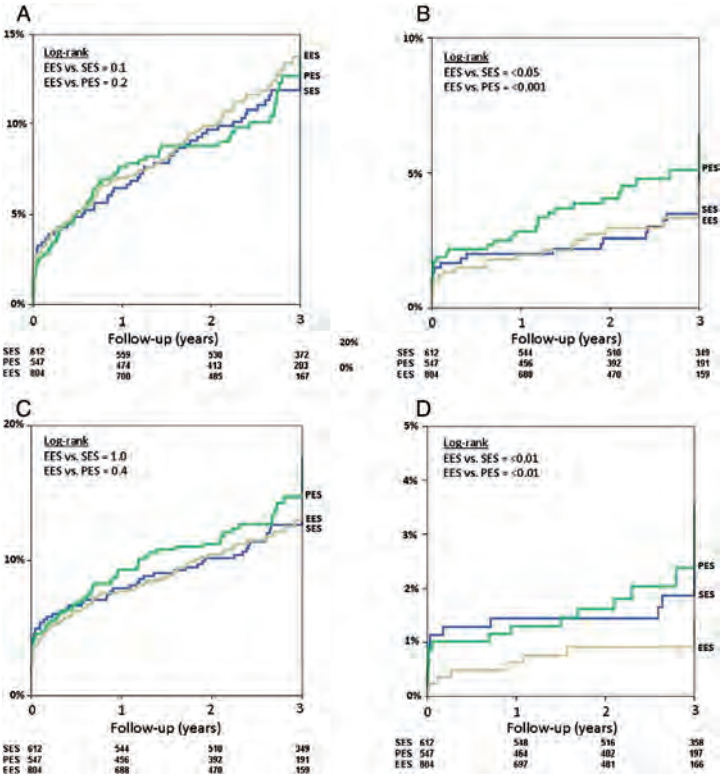

Fig. 2. Adjusted Kaplan–Meier curves according to stent type for the safety end points. The adverse cardiac event rates with the associated log-rank test for patients treated with SES, PES and EES: (A) all-cause mortality; (B) myocardial infarction; (C) cardiac death/myocardial infarction; (D) definite stent thrombosis. The numbers under the figures are the "patients at risk" at that certain time-point of the follow-up.

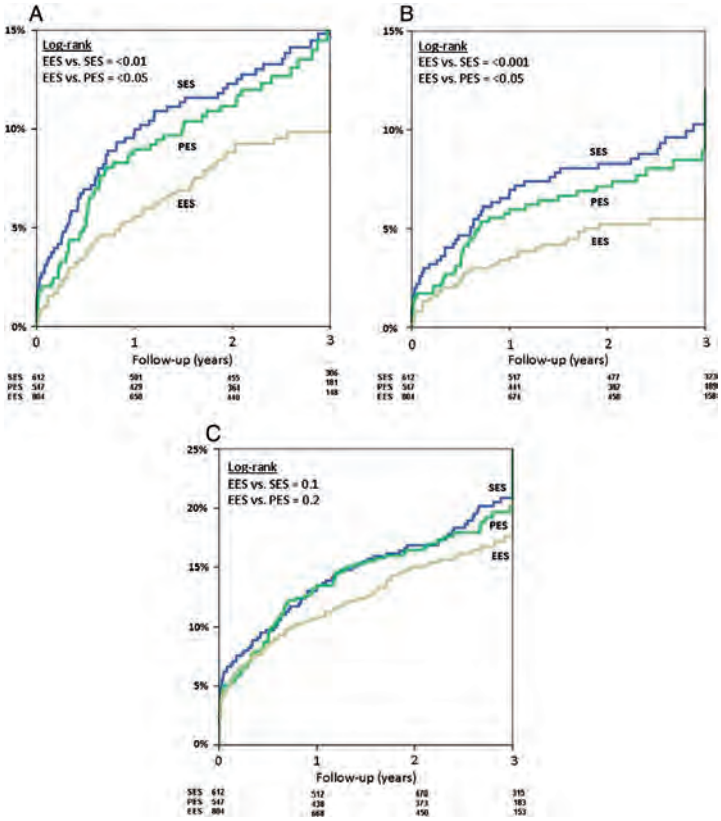

Fig. 3. Adjusted Kaplan–Meier curves according to stent type for the efficacy end points. The adverse cardiac event rates with the associated log-rank test for patients treated with SES, PES and EES: (A) TVR; (B) TLR; (C) MACE.

study had shown clinical superiority of EES over SES and PES in the diabetic population. In the present study, we established that EES are safer and more efficacious than PES and SES in the diabetic population. In terms of efficacy this effect is more evident in the non-insulin diabetics compared to the insulin-dependent diabetics.

Table 4
The usage of antiplatelet medication at the timepoint of definite stent thrombosis.

	All (n = 1963)	EES (n = 804)	SES (n = 612)	PES (n = 547)	p
ARC definite ST, n	51	8	23	20	
Complete data on medication At time of ST, n	46	8	20	18	
On DAPT at ST, n (%)	21 (45.7)	2 (25.0)	12 (60.0)	7 (38.9)	0.9
Aspirin at ST, n (%)	42 (91.3)	7 (87.5)	17 (85.0)	18 (100.0)	0.2
Clopidogrel at ST, n (%)	21 (45.7)	2 (25.0)	12 (60.0)	7 (38.9)	0.2
On neither antiplatelet at ST, n (%)	4 (8.7)	1 (12.5)	3 (15.0)	0 (0.0)	0.2

A comprehensive network meta-analysis of more than 50,000 patients showed not only that patients treated with EES had lower ST rates compared to earlier generation drug-eluting stents but even when compared to bare-metal stents at 2-year follow-up [19]. However, the diabetic population was not described in detail in this meta-analysis, making it impossible to draw conclusions on the safety and efficacy parameters of early and new-generation stent types in diabetic patients. More specifically, the analysis for diabetes populations included in the pooled meta-analysis by Palmerini et al. was limited to confirmation of the superiority of EES against other stent types, in terms of definite stent thrombosis, when this population was excluded. In addition, since patients in clinical trials, and therefore meta-analysis, are carefully selected, they do differ from patients in normal clinical practice. As a result it is important to confirm findings in “real-world” populations. Third, in view of the phenomenon of very late stent thrombosis, we not only assessed the incidence at two-years but add data to the existing literature for longer follow-up to three-years. In the selection of the stent type, the interventional cardiologist does not only consider

but also evaluate other performance measures. For this reason, we additionally provide data on overall performance measures of EES compared to other stent types. Differences in duration of dual antiplatelet therapy have been implicated as a main factor contributing to this, with recent PCI-patients prescribed dual antiplatelet therapy for at least 12 months. However, in our population we notice a lower rate of ST already in the early stages, when dual antiplatelet therapy use is comparable between the patients.

4.1. Study limitations

"Real-world" registries are a good manner to reflect the complex health situation of most patients, however there remains several limitations that needs to be acknowledged and addressed. First of all this was a non-randomized study resulting in cohorts with differences in baseline, procedural characteristics, antiplatelet treatment duration and follow-up duration. Although statistical corrections have been used to account for these differences, it remains arguable whether this was sufficient.

Second, the exact duration of clopidogrel use after percutaneous coronary intervention could not reliably be assessed and therefore the analysis are based on the prescribed duration of clopidogrel. In addition, it could be possible that some cases of ST were undetected in our study despite our attempts of an active surveillance. To avoid underestimation and overestimation of the occurrence of ST, the composite of definite ST and probable ST was provided in addition to the secondary ischemic end points, such as TLR and cardiac death. Third, the EES group consisted of 804 patients treated with the XIENCE V™ stent (Abbott Vascular, Santa Clara, CA) or the PROMUS™ stent (Boston Scientific, Natick, MA, USA). Although both stent have the same antiproliferative drug coating, the stent platforms have distinct features. Finally, cardiac events could have been missed due to the fact that data collection relied on the ability of the patient to remember events of the past year.

5. Conclusion

In diabetic patients, the unrestricted use of EES appears to be associated with improved outcomes, specifically a significant decrease in the occurrence of ST and in the need for TLR compared to early generation SES and PES throughout 3-year follow-up. No differences were observed for the other safety end points. These results should be interpreted in light of the inherent limitations of registry data.

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The influence of optimal medical treatment on the 'obesity paradox', body mass index and long-term mortality in patients treated with percutaneous coronary intervention: a prospective cohort study.

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The influence of optimal medical treatment on the 'obesity paradox', body mass index and long-term mortality in patients treated with percutaneous coronary intervention: a prospective cohort study

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ABSTRACT

Objective: To assess whether the obesity paradox persists in the long term and to study the effect of optimal medical treatment on this phenomenon.

Design: A retrospective cohort study.

Setting: A tertiary care centre in Rotterdam.

Participants: From January 2000 to December 2005, 6332 patients undergoing percutaneous coronary intervention for coronary artery disease were categorised into underweight (body mass index (BMI)<18.5), normal (18.5–24.9), overweight (25–29.9) and obese (>30).

Primary outcome measure: Mortality.

Secondary outcome measures: Cardiac death and non-fatal myocardial infarction.

Results: Optimal medical treatment was more common in obese patients as compared with normal weight patients (85% vs 76%; p<0.001). At a mean of 6.1 years, overweight and obese patients had a lower risk of all-cause mortality (HR: 0.75, 95% CI 0.66 to 0.86 and HR: 0.72, 95% CI 0.60 to 0.87, respectively). After adjusting for OMT in the multivariate analysis, BMI did not remain an independent predictor of long-term mortality (HR: 0.90, 95% CI 0.72 to 1.12 and HR: 1.07, 95% CI: 0.80 to 1.43, respectively).

Conclusion: BMI is inversely related to long-term mortality in patients treated with percutaneous coronary intervention. Patients with a normal BMI are on suboptimal medical treatment when compared with those with a high BMI. A more optimal medical treatment in the obese group may explain the observed improved outcome in these patients.

ARTICLE SUMMARY

Article focus

- Whether the obesity paradox persists in the long term.
- The effect of optimal medical treatment (OMT) on this phenomenon.

Key messages

- Body mass index (BMI) is inversely related to long-term mortality in patients treated with percutaneous coronary intervention.
- Patients with a normal BMI are on suboptimal medical treatment when compared with those with a high BMI.
- A more optimal medical treatment in the obese group may explain the observed improved outcome in these patients.

Strengths and limitations of this study

- Strengths of this study are that we examine the long-term effects of BMI on outcome and we try to explore the mechanisms of the obesity paradox. Limitations of the study are that we cannot prove the mechanism with an observational study and that details about OMT, such as duration of therapy and medication adherence, are lacking.

The increasing incidence of obesity in the industrialised world is a major public health concern. An increased body mass index (BMI) is associated with a higher mortality rate in the general population, and obesity is also well known as an independent risk factor for the development of cardiovascular disease.[1 2] However, several studies have shown that cardiovascular patients who are overweight or obese have a better outcome than patients with a normal weight.[3 4] Indeed, the greatest mortality rates are observed in patients with a very low BMI (<18.5 kg/m^2) and this phenomenon has been termed the 'obesity paradox'.[3–5]

Most studies examining the role of BMI on mortality in patients treated with percutaneous coronary intervention (PCI) have focused on the short-term effects,[6–10] while only a few studies examined the impact of BMI on long-term mortality.[11–14] While many studies have examined the obesity paradox, only a few studies explored the mechanisms of this phenomenon.[4 15 16] A more aggressive lifestyle modification and optimisation of medical treatment may be a plausible reason for the enhanced survival in individuals who are obese at the time of coronary revascularisation.

Hence, the aims of this study were (1) to evaluate the effect of BMI on long-term mortality in a consecutive series of patients treated with PCI and (2) to determine whether a difference in the use of optimal medication at follow-up between the different BMI groups is a contributing factor for the obesity paradox.

METHODS

Study population

Between 1 January 2000 and 31 December 2005, a total of 7217 PCI's were performed in our institution. Bare metal stents were used exclusively in 2681 PCI's performed between January 2000 and 15 April 2002. Subsequently, 1035 interventions were performed between 16 April 2002 and 23 February 2003, using sirolimus-eluting stents (Cypher®; Cordis Corp., Johnson & Johnson, Warren, New Jersey, USA), as part of RESEARCH registry.[17] The following 3339 interventions from 23 February 2003 to 31 December 2005 were performed using paclitaxel-eluting stents (TAXUS Express2 or Liberté; Boston Scientific, Natick, Massachusetts, USA), as part of the T-SEARCH registry.[18] Only patients (n=6332) with registered baseline weight and height were eligible for inclusion in the current study. The study was performed in line with ethical guidelines in accordance with the Declaration of Helsinki.

Baseline data

Demographic variables included gender, age, height and weight. Information on clinical variables (ie, dyslipidaemia, hypertension, smoking, diabetes mellitus, family history of coronary artery disease (CAD), indication for PCI, previous myocardial infarction (MI), previous coronary artery bypass graft surgery, previous PCI, multivessel disease and left ventricular ejection fraction (LVEF)) were prospectively collected at the time of the procedure and recorded in the institutional database. Dyslipidaemia was defined as total cholesterol levels ≥240 mg/dl (6.21 mmol/l) or if the patient was on lipid-lowering medication. Hypertension was defined as blood pressure >140/90 mm Hg or if a patient was being treated with antihypertensive drugs. Diabetes mellitus was defined in patients being treated by oral antiglycaemic agents or insulin.

Body mass index

BMI was defined as weight in kilograms divided by the square of the height in metres. In our institution, height and weight are self-reported unless the patient does not know in which case this is performed in the referral clinic. Categorisation of BMI was adopted from WHO and the National Institutes of Health[19] and defined as underweight (BMI <18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and obese (≥30 kg/m^2).

Outcome

End points were all-cause mortality, cardiac death and non-fatal MI, and major cardiac events (a composite of cardiac death or non-fatal MI). Cardiac death was defined as death from any cardiac cause including sudden cardiac death, MI, congestive heart failure, cardiac arrhythmias and death in which there is evidence of a primary cardiac cause that could not be classified as mentioned above. Sudden cardiac death was defined as unexpected natural death due to cardiac causes within 1 h of onset of acute symptoms. Criteria of MI diagnosis included two or more of the following: (1) typical chest pain lasting for more than 20 min, (2) development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms in two contiguous ECG leads), (3) elevated levels of serum markers for cardiac necrosis (creatine kinase (CK) >2 or CK-MB level >3 times the upper limit of normal).

Information about the in-hospital outcome was obtained from an electronic clinical database maintained at our institution and by review of the hospital records for those transferred to other hospitals. In-hospital outcomes are included in the 6-year outcome. Post-discharge survival status was obtained from the Municipal Civil Registries. Questionnaires with information about anginal status, repeated hospital admissions, revascularisation procedures and medication use were sent to all living patients on a yearly basis. The hospital records, referring physicians and institutions were consulted for additional information whenever necessary. Events were adjudicated by two independent cardiologists according to criteria defined above.

Optimal medical treatment

We defined optimal medication as the use of three or more (since some of the patients may be intolerant to one of the medications) of the four types of medication (aspirin, β blockers, statins, ACE inhibitors/angiotensin II receptor blockers) known to improve prognosis in patients with CAD according to ACC/AHA guidelines.[20]

Statistical analysis

Categorical variables were compared with the χ^2 test and continuous variables with analysis of variance. Univariable and multivariable Cox proportional hazard regression analyses were used to examine the relation between BMI and the defined end points. All BMI classes were entered into the model, with normal weight patients (BMI 18.5–24.9 kg/m^2) as the reference. Multivariable analysis was adjusted for all baseline characteristics,

which were available for all patients included in the study. Optimal medical treatment was added to the model to assess its importance as an independent predictor. Kaplan–Meier curves were generated to graphically present the time to death for patients in the different BMI groups. Additionally univariate and multivariate Cox regression analysis was performed with BMI as a continuous variable to determine the relation of an increase in 1 kg/m^2 and the primary end point. The effect of the introduction of optimal medical treatment (OMT) on the model was tested as in the models with BMI as a categorical variable. Landmark Cox regression analysis at 2-year follow-up was performed to assess for changes in predictors of the end point mortality and to determine the effect of OMT on late outcome.

Patients lost to follow-up were considered at risk until the day of final contact, at which point they were censored. The log-rank test was used to ascertain whether differences between groups were statistically significant. All tests were two tailed and a probability value of <0.05 was considered statistically significant. For Cox proportional hazard regression analyses, HRs and their corresponding 95% CIs were reported. All data were analysed using SPSS V.17.0 for Windows (SPSS Inc.).

RESULTS

Follow-up on survival status was available for 98% of patients. The average follow-up time was 6.1 years (range 3–11 years). In total, there were 1059 deaths (17%) of which 454 (43%) were cardiac.

The small size (n=35) of the underweight group precludes any reliable analyses and the group was therefore excluded. Patient baseline characteristics and clinical data according to the three BMI categories are shown in table 1. Obese patients tended to be younger, and although the overall population was predominantly comprised of men, gender was more equally represented in the obese group. Dyslipidaemia, hypertension and diabetes mellitus were more common in the obese group, while current smoking was more prevalent in the normal weight group.

The different types of medication used at follow-up according to the three BMI categories are shown in table 2. Obese patients tended to use more β blockers and ACE inhibitors compared with the normal weight group resulting in more optimal medical treatment at follow-up in the obese group.

Univariate and multivariate associations between BMI and long-term outcome are presented in table 3. Clinical characteristics that had a significant association on multivariate analysis were age, gender, diabetes mellitus, multivessel disease and LVEF. In univariate analyses, overweight and obese patients had more favourable long-term outcomes in terms of all-cause death (HR: 0.72, 95% CI 0.63 to 0.82 and HR: 0.61, 95% CI 0.51 to 0.74, respectively) and cardiac death (HR: 0.77, 95% CI 0.63 to 0.94 and HR: 0.73, 95% CI 0.56 to 0.95,

Table 1 Baseline characteristics

	BMI (kg/m^2)				
Variable	**Total (n=6297)**	**18.5–24.9 (n=2095)**	**25–29.9 (n=2956)**	**>30 (n=1246)**	**p Value**
Male, n (%)	4562 (72)	1466 (70)	2266 (77)	830 (67)	<0.001
Age ± SD	61±11.4	62±12.2	62±11.2	59±10.4	<0.001
BMI ± SD	27.0±4.0	23.11±1.5	27.23±1.4	33.0±3.1	<0.001
Cardiovascular history, n (%)					
Previous MI	2128 (34)	686 (33)	1011 (34)	431 (35)	0.448
Previous CABG	692 (11)	200 (10)	354 (12)	138 (11)	0.025
Previous PCI	1630 (26)	513 (25)	764 (26)	353 (28)	0.049
Multivessel disease	3437 (55)	1122 (54)	1635 (55)	680 (55)	0.47
Risk factors, n (%)					
Dyslipidaemia	4759 (76)	1531 (73)	2246 (76)	982 (79)	0.001
Hypertension	2554 (41)	714 (34)	1161 (39)	679 (55)	<0.001
Family history	1921 (31)	623 (30)	895 (30)	403 (32)	0.27
Current smoker	1512 (24)	561 (27)	661 (22)	290 (23)	0.001
Diabetes mellitus	1057 (17)	251 (12)	466 (16)	340 (27)	<0.001
Indication for PCI, n (%)					0.006
Stable angina	3059 (49)	965 (46)	1450 (49)	644 (52)	
Unstable angina	2084 (33)	707 (34)	971 (33)	406 (33)	
Acute MI	1154 (18)	423 (20)	535 (18)	196 (16)	
LVEF*, n (%)					0.603
Good	3052/3763 (81)	1013/1266 (80)	1442/1757 (82)	597/740 (81)	
Impaired	711/3763 (19)	253/1266 (20)	315/1757 (18)	143/740 (19)	

*Data for this characteristic were not available in all patients.
BMI, body mass index; CABG, coronary bypass graft surgery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2 Medication at follow-up

Variable	BMI (kg/m^2) Total (n=6297)	18.5–24.9 (n=2095)	25–29.9 (n=2956)	>30 (n=1246)	p Value
Medication, n (%)					
Aspirin	5352 (85)	1366 (85)	2014 (85)	825 (86)	0.979
β blocker	5038 (80)	1246 (78)	1883 (80)	832 (86)	<0.001
Statin	5793 (92)	1451 (91)	2163 (92)	898 (93)	0.092
ACE inhibitor	3149 (50)	775 (48)	1154 (49)	547 (57)	<0.001
Optimal medication*, n (%)	4975 (79)	1219 (76)	1839 (78)	818 (85)	<0.001

*Defined as the use of three or more of the four types of medication.
BMI, body mass index.

respectively). (table 3, figure 1) Overweight patients also showed a lower risk for the composite end point of cardiac death and non-fatal MI (HR: 0.84, 95% CI 0.71 to 0.99). Most of these differences remained significant after multivariate adjustments for all baseline characteristics. However, the lower incidence of cardiac death in obese patients did not remain significant after multivariate analysis. Moreover, when adjusting for baseline characteristics and optimal medication at follow-up, overweight and obese patients had a equal long-term survival (HR: 0.90, 95% CI 0.72 to 1.12 and HR: 1.07, 95% CI 0.80 to 1.43, respectively) compared with the normal weight group.

In a model with BMI as a continuous variable, one unit increase in BMI showed HR 0.95 (95% CI 0.93 to 0.97), p<0.001, adjusted HR 0.96 (95% CI 0.95 to 0.98), p<0.001. When OMT was introduced in the model, the relation did not remain significant: HR 1.00 (95% CI 0.98 to 1.03), p=0.81.

For the whole population, OMT had HR 0.63, for the normal population 0.60, for the overweight 0.64 and for the obese 0.69.

In a landmark analysis at 2 years, multivariate predictors of late outcome included gender, BMI, age, hypercholesterolaemia, diabetes mellitus, family history of CAD, previous coronary artery bypass graft surgery and LVEF.

The introduction of OMT in the 2-year landmark Cox regression model also altered the significance of BMI from overweight versus normal (HR: 0.806, 95% CI 0.678 to 0.960, p=0.015) and obese versus normal (HR: 0.840, 95% CI 0.661 to 1.067, p=0.152) in the model without OMT to overweight versus normal (HR: 0.911, 95% CI 0.722 to 1.149, p=0.429) and obese versus normal (HR: 1.122, 95% CI 0.819 to 1.537, p=0.472) in the model with OMT.

The individual medications were analysed in a separate Cox regression model and statin use showed the strongest independent protective effect on long-term mortality, statins HR 0.60 (95% CI 0.46 to 0.78), p<0.0001. All the other three medications also showed independent protective effect as follows: aspirin HR 0.75 (95% CI 0.60 to 0.95), p=0.014, β blocker HR 0.83 (95% CI 0.66 to 1.04), p=0.109, and ACE inhibitors HR 0.84 (95% CI 0.69 to 1.03), p=0.093.

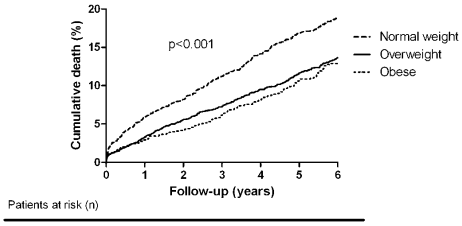
DISCUSSION

This study confirms the validity of the 'obesity paradox' with an inverse relation in all-cause mortality and BMI of

Table 3 HRs of study end points

	Events	Univariate HR (95% CI)	p Value	Multivariate* HR (95% CI)	p Value	Multivariate† HR (95% CI)	p Value
All-cause mortality							
Overweight	456 (15%)	0.72 (0.63 to 0.82)	<0.001	0.75 (0.66 to 0.86)	<0.001	0.90 (0.72 to 1.12)	0.335
Obese	159 (13%)	0.61 (0.51 to 0.74)	<0.001	0.72 (0.60 to 0.87)	0.001	1.07 (0.80 to 1.43)	0.663
Cardiac death							
Overweight	198 (7%)	0.77 (0.63 to 0.94)	0.011	0.81 (0.66 to 0.99)	0.044	1.05 (0.71 to 1.57)	0.800
Obese	77 (6%)	0.73 (0.56 to 0.95)	0.019	0.82 (0.62 to 1.08)	0.152	1.02 (0.60 to 1.75)	0.939
Non-fatal MI							
Overweight	138 (5%)	0.81 (0.63 to 1.04)	0.095	0.79 (0.61 to 1.01)	0.056	0.75 (0.57 to 0.98)	0.036
Obese	79 (6%)	1.12 (0.84 to 1.49)	0.434	1.03 (0.77 to 1.38)	0.844	0.88 (0.63 to 1.24)	0.472
Cardiac death or non-fatal MI							
Overweight	336 (13%)	0.84 (0.71 to 0.99)	0.038	0.83 (0.70 to 0.99)	0.033	0.95 (0.74 to 1.21)	0.658
Obese	156 (15%)	0.87 (0.70 to 1.07)	0.186	0.87 (0.69 to 1.08)	0.202	0.94 (0.68 to 1.30)	0.722

*Adjusted for all baseline characteristics.
†Adjusted for all baseline characteristics and optimal medication.
MI, myocardial infarction.



Patients at risk (n)

Normal weight	2095	1947	1877	1765	1527	1256	935
Overweight	2956	2833	2735	2614	2269	1879	1431
Obese	1246	1197	1166	1099	919	727	543

Figure 1 Kaplan–Meier survival curve for all-cause mortality in normal weight, overweight and obese patients at 6-year follow-up.

patients undergoing percutaneous revascularisation in the long term up to 6 years. Patients with higher BMI at baseline have more optimal medical treatment, which may explain the reduction in mortality as observed in these patients up to this time point.

In the current study, we found that the inverse relation between BMI and mortality persists during long-term follow-up of patients treated with PCI. The overweight and obese groups showed almost 30% lower mortality than patients with a normal BMI.

In this population, crude death rate was 17% during a mean follow-up of 6 years. Cardiac deaths were responsible for 43% of all deaths. As expected, comorbid conditions (eg, dyslipidaemia, hypertension and diabetes mellitus) were more prominent in the obese population.

Several other studies have shown a paradoxical effect of moderate obesity on outcome after PCI.[6–12] They also found significantly worse outcomes in patients with a BMI >30 or <20 kg/m^2. These results were echoed in a large meta-analysis by Romero-Corral *et al*[21] who included studies with a total of 250 152 patients undergoing PCI or coronary artery bypass grafting. In fact, overweight and obese patients with coronary heart disease had a lower risk for total and cardiovascular mortality compared with underweight and normal weight patients with coronary heart disease. Our study results are in line with these findings; however, while the duration of the follow-up period in most of these studies was restricted to 1 year, that period was extended to 6 years in the current study.

The reason for the paradoxic U- or J-shaped relation between BMI and adverse outcome is not yet understood. Several explanations for this phenomenon have been suggested. Peripheral adiposity confers cardiovascular benefits due to the secretion of adiponectin, which has anti-inflammatory, insulin-sensitising and antiatherogenic effects. Also, these patients seem to have a lower total body fat content, which implies that subcutaneous body fat is relatively 'inert' in metabolic and inflammatory/mediation terms.[22] Furthermore, it has been suggested that hypercholesterolaemia and high levels of serum low-density lipoproteins associated with obesity serve a scavenging action against unbound circulating lipopolysaccharides with consequent anti-inflammatory response and improved long-term outcome.[23]

Studies of the BMI–mortality relationship may suffer from several sources of bias and confounding which can explain the U- or J-shaped relationship in some of these studies. Reverse causality can be present if thin people are disproportionately more susceptible to disease and suffer worse health outcomes than those with higher BMI levels. Another important consideration is potential overcontrolling by adjustment for cardiovascular risk factors associated with increased weight.[24 25] If BMI contributes to the development of a risk factor, statistical adjustment for such risk factors could be misleading with regard to the contribution of BMI. Besides these methodological and conceptual issues, there are several potential modifiers of the BMI–mortality association. This association may vary according to variables such as sex, ethnicity, age and body fat distribution. Another major problem with BMI is that it is a surrogate, measuring total body mass. One explanation for a U-shaped relationship between BMI and mortality is that calculated BMI measures do not differentiate between fat and fat-free mass, which have opposite effects on health and longevity.[26]

In this study, the impact of differences in optimal medication, one of the implicated mechanisms of the obesity paradox, was explored. Strikingly, we did notice that optimal medical treatment was more common in the high BMI groups, likely a reflection of the higher incidence of risk factors in these subgroups. Our study supports the hypothesis that part of the obesity paradox may be mediated by the earlier and more complete secondary preventive medical treatment in the high BMI groups who present for revascularisation at a younger age.

Aspirin, statin, β blocker and ACE inhibitor use have all shown significant reduction in mortality in previous studies.[27] In our study cohort, patients with a higher BMI were more often on β blocker and ACE inhibitor treatment when compared with subjects with normal weight. The positive effect on survival in the long-term of such drug treatment is an important contributor to the apparent survival advantage that is observed in patients with a high BMI. Thus, at least in part, OMT explains the obesity paradox. Moreover, our study highlights the importance of optimising medical treatment and encouraging compliance even in patients with good symptom control achieved after percutaneous revascularisation for CAD.

The beneficial effect of OMT in the higher BMI group may have been influenced by a change in lifestyle. The change in BMI over time and measures other than OMT such as exercise and dieting may have contributed to the improved long-term prognosis in these patients.

Baseline clinical characteristics of patients with a high BMI suggest that these patients have a higher risk profile compared with those with normal or low BMI. Clearly, patients with high BMI undergoing PCI have a more optimal medical treatment. Whether more active screening related to the obesity and cardiovascular risk factors is leading to a more timely and aggressive pharmacological and/or mechanical intervention in this population remains to be established.

In an era of stent implantation as a mainstream treatment for CAD, stent-related factors may also influence the impact of BMI on clinical outcome. Although in our study we were not interested in stent-related outcomes such as stent thrombosis and stent restenosis with target lesion revascularisation, these two may play a role in hard end points especially in the long term. Patients with a high BMI have been shown to have higher rates of target vessel revascularisation possibly reflecting more aggressive neointimal hyperplasia in the stent, progressive disease in the treated vessel or a combination of the two.[14] The coexisting cardiovascular risk factors (hypertension, dyslipidaemia and particularly diabetes mellitus) in these patients are thought to play a major role in these mechanisms of target vessel failure. Stent thrombosis has an even more direct effect on hard end points since it causes an MI and sometimes sudden cardiac death even before presentation. Patients with a high BMI are thought to be at a higher risk possibly due to suboptimal dosing of dual antiplatelet treatment.[14] Thus, although stent-related factors can potentially influence the relation of BMI and outcome, the mechanisms implicated do not support the obesity paradox that we observe.

The current study has a number of limitations that need to be highlighted. Data regarding waist circumference and waist/hip ratio that measures abdominal obesity were not routinely available. A more precise differentiation between peripheral adiposity and central compartment adiposity would have served to support the suggested hypothetical explanation about the role of a high BMI in prolonging survival in our patient population. Regarding the detection of our end points, a number of non-fatal and/or asymptomatic or silent MIs might have not been reported, especially if these occurred outside the hospital. Noting that in patients who have a contraindication to a treatment option (eg, β blockers), the lack of benefit from this treatment is not physician induced but determined by the patient's condition, which may itself put the latter in a higher risk category. This will in the future need to be addressed in a prospective study. Clinical measurement, rather than self-reported height and weight, would have provided a more accurate BMI data, eliminating any possible bias. OMT was defined according to patient medication at first time of contact but no information of duration or compliance of such treatment was available. Objective parameters of lifestyle modifications and risk factor control would shed light on the importance of such an intervention on clinical outcome.

In conclusion, the results of the current study show that BMI is inversely related to long-term mortality in patients treated with PCI. Patients with a low BMI are on suboptimal medical treatment when compared with those with a high BMI. However, a more optimal medical treatment in the obese group may explain the improved outcome in these patients.

Contributors LS, MM, RMO, ML, PdJ, R-JvG, PWS and RTvD took part in the interpretation of findings and in drafting the manuscript. LS did the statistical analyses. LS, MM, PdJ, R-JvG, PWS and RTvD contributed to the data collection. LS, MM and RTvD took main responsibility for conception and design and for writing of the manuscript. PWS was the primary investigator of the trial. All authors made an final approval of the version to be published.

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Competing interests None.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Further information and details on the prospective percutaneous coronary intervention registry data from which this study is derived is available at request from the Erasmus University Medical Centre, Rotterdam, the Netherlands.

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4.3 Impact of renal insufficiency on safety and efficacy of drug-eluting stents compared to bare-metal stents at 6 years.

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Impact of Renal Insufficiency on Safety and Efficacy of Drug-Eluting Stents Compared to Bare-Metal Stents at 6 Years

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Background: There is few information on the long-term efficacy and safety of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) compared to bare metal stents (BMS) in all-comer percutaneous coronary intervention (PCI)—patients complicated by renal insufficiency (RI). Objective: Our aim was to assess the 6-year clinical outcome of PCI-patients with RI treated exclusively with BMS, SES, or PES in our academic hospital. Methods: A total of 1382 patients, included in three cohorts of consecutive PCI-patients (BMS = 392; SES = 498; PES = 492), were categorized by creatinine clearance calculated by the Cockroft–Gault formula (normal kidney function $\geq$ 90; mild RI = 60–89; moderate RI < 60) and systematically followed for the occurrence of major adverse cardiac events (MACE). Results: Mortality rates were significantly higher for patients with moderate RI compared to mild RI and normal kidney function at 6 years (Kaplan–Meier estimate: moderate RI (34%) vs. mild RI (12%), $P < 0.001$; moderate RI (34%) vs. normal kidney function (8%), $P < 0.001$). After multivariate Cox-regression analysis, SES and PES decreased the occurrence of target-vessel revascularization (TVR) and MACE at 6 years in patients with a normal creatinine clearance compared to BMS [adjusted hazard ratio (aHR) = 0.48, 95% CI: 0.28–0.84; aHR = 0.75, 95% CI: 0.57–0.97, respectively] with no significant effect on mortality. Safety- and efficacy end points were comparable for the three stent types in patients with mild- and moderate renal function. Conclusion: Patients with a normal creatinine clearance had significant improvement in TVR and MACE rates after SES- or PES implantation compared to BMS at 6 years. However, there was no superiority of both drug-eluting stents over BMS in safety and efficacy end points for patients with impaired renal function.

Key words: stents; kidney function; percutaneous coronary intervention

INTRODUCTION

More than 20% of the patients undergoing percutaneous coronary intervention (PCI) have impaired renal function, which has been associated with higher morbidity and mortality rates post-PCI [1–3]. In fact, a recent pooled-analysis of 5-year data from three randomized trials (SIRIUS, C-SIRIUS, and E-SIRIUS), including 1,510 patients, showed that patients with moderate RI (GFR < 60 ml/min) had significantly worse mortality rates compared to patients with mild RI and normal kidney function at 1- and 5-years follow-up [4]. Moreover, the implantation of sirolimus-eluting stent (SES) seems to reduce angiographic reste-

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nosis and target-vessel revascularization (TVR) rates compared to bare metal stent (BMS) independent of the degree of RI [5]. In addition, also paclitaxel-eluting stents reduced angiographic restenosis rates and target lesion revascularization rates at 1 year in patients with RI compared to BMS in the TAXUS-IV trial [6].

Although it has been proven that drug-eluting stents (DES) decrease in-stent restenosis and subsequently TVR rates compared to BMS in randomized trials, the exclusion of high risk patients such as those with severe renal impairment limit the applicability of these results to "real-world" patients. For instance, the possibility of a higher incidence of (very late) stent thrombosis with DES-implantation in patients with RI should be taken into consideration. Therefore, whether the net benefits hold true for patients with RI in the short- and long-term remains unknown [7–13]. Thus, we set out to explore the long-term safety and efficacy of sirolimus-eluting stents or paclitaxel-eluting stents compared to bare-metal stents in patients with RI in the "real world."

METHODS

Patient Population and Study Design

From April 2002 until October 2002, our policy was to treat all PCI-patients ($n = 508$) with only SES (Cypher®, Cordis Corp., Johnson & Johnson, Warren, NJ) as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry [14]. Between February 2003 and September 2003, a total of 576 PCI-patients were treated with the paclitaxel-eluting stent (PES; TAXUS™, Express2™, or Liberté™, Boston Scientific, Natick, MA) during the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry [15]. For comparison, a control group was composed of 450 BMS-patients, which were treated from October 2001 until March 2002. Among these patients of the three cohorts, 1,382 patients (90%) had a baseline serum creatinine measured in our institution and comprised the study population (BMS = 392; SES = 498; PES = 492).

All procedures were performed according to standard clinical guidelines, and every patient was pretreated with aspirin and $\geq$300 mg of clopidogrel. The postprocedural dual antiplatelet regimen consisted of $\geq$80 mg aspirin lifelong and $\geq$75 mg clopidogrel for at least 1 month if BMS were used, $\geq$3 months for patients with SES, and $\geq$6 months for patients with PES. Periprocedural glycoprotein IIb/IIIa antagonists were used at the discretion of the treating interventional cardiologist. All the repeat coronary angiographies were clinically driven by physical symptoms or diagnostic findings suggestive of myocardial ischemia.

Renal Function Evaluation

The baseline creatinine values were used to calculate the creatinine clearance according to the Cockroft and Gault formula: creatinine clearance (millilitres/minute) = (140-age) $\times$ weight (kilograms) $\div$ 72 $\times$ serum creatinine (milligrams/decilitre) ($\times$0.85 for women). Patients were categorized into three groups in accordance with the guidelines of the National Kidney Foundation for staging chronic kidney disease (CKD) based on glomerular filtration rate: Group 1, normal kidney function (creatinine clearance $\geq$ 90 ml/min); Group 2, mild RI (creatinine clearance = 60–89 ml/min); and Group 3, moderate RI (creatinine clearance $<$ 60 ml/min).

Clinical Endpoints and Definitions

The primary end point was the occurrence of all-cause mortality. Secondary end points included TVR, all-cause mortality/MI, major adverse cardiac events (MACE) [defined as a composite of all-cause mortality, myocardial infarction (MI) and TVR], and stent thrombosis.

TVR was defined as a repeat PCI in the same vessel as the index procedure in the presence of ischemic symptoms or positive functional ischemia study on the target vessel area and a significant minimal luminal diameter stenosis of at least 50%. MI was diagnosed by recurrent typical clinical symptoms, the development of ST-segment elevation or left bundle branch block on electrocardiography with a CK-MB rise of three times the upper limit of normal and/or positive troponin levels in the laboratory values. Definite stent thrombosis was defined as an angiographically documented thrombus in or within 5 mm of the stent, accompanied by at least one of the following criteria as recommended by the academic research consortium criteria: (1) acute symptoms; (2) ischemic ECG changes; and (3) typical rise and fall of cardiac markers and categorized into early (within 30-days poststent implantation), late (within 30 days and 1-year poststent implantation), and very late (after 1 year poststent implantation).

Follow-Up

The clinical status of the patients was documented once a year by contacting municipal civil registries until December 2009. A health-related questionnaire, consisting of queries regarding rehospitalization and cardiac events, was send to all living patients. The hospital records and coronary angiographies from our academic hospital or the referring institution were systematically reviewed in case of a patient-reported event.

TABLE I. Baseline and Procedural Characteristics Stratified According to Renal Function and Stent Type

	Group 1	Group 2	Group 3	
	≥90	60–89	<60	
Number of patients	$n = 615$	$n = 520$	$n = 247$	P
Characteristics stratified according to renal function				
Demographic characteristics				
Age, years (± SD)	54.6 (± 9)	64.6 (± 9)	72.2 (± 8)	<0.001
Male (%)	84.2	63.7	51.0	<0.001
Cardiac history (%)				
Prior MI	33.1	36.6	36.1	0.4
Prior CABG	4.7	8.5	15.8	<0.001
Prior PCI	17.4	21.0	19.9	0.3
Risk factors (%)				
Current smoking	39.0	27.1	18.2	<0.001
Hypertension	36.3	41.0	53.4	<0.001
Hypercholesterolemia	59.7	56.2	56.7	0.5
Diabetes	16.4	16.2	21.9	0.1
Insulin dependent	5.0	4.2	7.3	0.2
Noninsulin dependent	11.5	11.9	14.6	0.5
Family history	38.2	31.5	30.0	0.02
Clinical presentation (%)				
Stable angina	42.9	51.9	47.4	0.01
Unstable angina	31.1	32.7	38.5	0.10
Acute myocardial infarction	25.9	15.4	13.8	<0.001
Cardiogenic shock	1.6	1.7	4.0	0.06
Disease severity				
Multivessel disease (%)	50.1	50.2	68.8	<0.001
Bifurcation (%)	13.8	14.6	12.1	0.7
Number of stents (± SD)	2.0 (± 1.2)	2.1 (± 1.4)	2.3 (± 1.5)	0.02
Average stent diameter, mm (± SD)	3.0 (± 0.3)	3.0 (± 0.3)	2.9 (± 0.4)	<0.001
Total stent length, mm (± SD)	36.9 (± 26)	37.8 (± 29)	46.8 (± 31)	0.2
Treated vessel (%)				
RCA	36.7	38.5	36.4	0.8
LAD	56.9	56.9	60.7	0.5
LCX	33.0	31.5	33.2	0.8
LM	2.8	3.7	4.0	0.6
Bypass graft	1.1	3.1	8.1	<0.001
AHA lesion class (%)				
Type A	16.4	16.7	15.4	0.9
Type B1	31.1	27.5	28.3	0.4
Type B2	45.4	54.4	54.3	<0.01
Type C	44.9	35.4	42.5	<0.01
Stent type (%)				
BMS	28.5	27.9	29.1	0.9
SES	33.8	39.4	34.4	0.1
PES	37.7	32.7	36.4	0.2
Thrombocyte aggregration inhibitor				
Clopidogrel duration, months (± SD)	4.0 (± 2.3)	3.9 (± 2.4)	6.0 (± 0.0)	0.8
IIb/IIIa inhibitor (%)	28.5	23.1	23.1	0.2
Characteristics stratified according to stent type				
Demographic characteristics				
Age, years (± SD)	60.9 (± 11)	61.2 (± 11)	61.7 (± 11)	0.6
Male (%)	70.7	67.9	73.2	0.2
Cardiac history (%)				
Prior MI	39.5	30.5	35.8	<0.05
Prior CABG	8.4	9.4	6.5	0.2
Prior PCI	18.9	19.1	19.5	1.0
Risk factors (%)				
Current smoking	33.9	30.1	29.1	0.3
Hypertension	37.8	41.6	43.3	0.2

(Continued)

Table I. Baseline and Procedural Characteristics Stratified According to Renal Function and Stent Type (continued)

	Group 1	Group 2	Group 3	
	≥90	60–89	<60	
Number of patients	$n = 615$	$n = 520$	$n = 247$	P
Hypercholesterolemia	53.6	56.0	63.0	0.01
Diabetes	15.8	17.5	18.3	0.6
Insulin dependent	4.1	5.8	5.3	0.5
Noninsulin dependent	11.7	11.6	13.2	0.7
Family history	27.6	32.5	41.3	<0.001
Clinical presentation (%)				
Stable angina	49.2	45.0	47.6	0.4
Unstable angina	33.2	37.6	28.3	<0.01
Acute myocardial infarction	17.6	17.1	24.2	<0.01
Cardiogenic shock	2.0	1.6	2.6	0.5
Disease severity				
Multivessel disease (%)	48.7	54.4	56.3	0.1
Bifurcation (%)	6.9	15.7	17.5	<0.001
Number of stents (± SD)	1.8 (± 1.0)	2.1 (± 1.4)	2.2 (± 1.5)	<0.001
Average stent diameter, mm (± SD)	3.1 (± 0.3)	2.8 (± 0.2)	3.0 (± 0.4)	<0.001
Total stent length, mm (± SD)	29.8 (± 19)	38.8 (± 28)	43.4 (± 32)	<0.001
Treated vessel (%)				
RCA	33.2	39.0	39.0	0.1
LAD	58.9	58.4	55.7	0.6
LCX	32.7	31.5	33.3	0.8
LM	2.6	2.8	4.5	0.2
Bypass graft	2.0	3.4	3.7	0.3
AHA lesion class (%)				
Type A	20.2	21.9	7.7	<0.001
Type B1	32.1	31.1	25.0	<0.05
Type B2	47.4	48.8	54.3	0.1
Type C	30.6	41.8	48.2	<0.001
GFR (%)				
≥90	44.6	41.8	47.2	0.2
60–89	37.0	41.2	34.6	0.1
<60	18.4	17.1	18.3	0.8
Thrombocyte aggregration inhibitor				
Clopidogrel duration, months (± SD)	1.0 (± 0.1)	4.2 (± 2.0)	6.0 (± 0.0)	<0.001
IIb/IIIa inhibitor (%)	32.4	18.9	26.6	<0.001

Data are presented as percentages or means (± SD). AHA, American Heart Association; BMS, bare metal stent; CABG, coronary artery bypass graft; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; MI, myocardial infarction; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; RCA, right coronary artery; SD, standard deviation; SES, sirolimus-eluting stent.

Statistical Analysis

Categorical baseline variables were tested with the Chi-square test, and the ANOVA test was used to calculate the of-continuous baseline variables between the groups. The Kaplan–Meier method estimated the cumulative adverse cardiac events for the end points, and the differences between the three stent curves were tested with the log-rank test. Multivariate Cox proportional hazard regression model [95% confidence interval (CI) and P-value < 0.05 regarded as significant] was used to adjust for differences in baseline and procedural characteristics between the groups. All baseline variables with a P-value ≤ 0.5 in univariable analysis were used in the multivariate Cox proportional hazard regression model. Stepwise backward deletion of the least significant variable was performed until all variables had a P-value of ≤ 0.10.

Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All statistical analyses were performed with SPSS for Windows version 17 (SPSS, Chicago, IL).

RESULTS

Population Characteristics

The baseline and procedural characteristics of the three groups stratified according to renal function are shown in Table I. Patients with a creatinine clearance of less than 60 mL/min were on average older, more often hypertensive, had more prior coronary artery

TABLE II. Six-Year Crude Event Rates Stratified According to Renal Function

	Group 1	Group 2	Group 3	
	≥90 (n = 615)	60–89 (n = 520)	<60 (n = 247)	P
Creatinine clearance (ml/min)				
Mortality	62 (10.1%)	70 (13.5%)	93 (37.7%)	<0.001
Mortality/MI	101 (16.4%)	106 (20.4%)	99 (40.1%)	<0.001
MACE	159 (25.9%)	160 (30.8%)	117 (47.4%)	<0.001
TVR	91 (14.8%)	82 (15.8%)	32 (13.0%)	0.6
ST	20 (3.3%)	17 (3.3%)	5 (2.0%)	0.6
Early	5 (0.8%)	9 (1.7%)	2 (0.8%)	0.3
Late	7 (1.1%)	1 (0.2%)	0 (0.0%)	0.047
Very late	8 (1.3%)	7 (1.3%)	3 (1.2%)	1.0

MACE, Major Adverse Cardiac Events; MI, myocardial infarction; ST, stent thrombosis; TVR, target-vessel revascularization. Stent thrombosis occurring within 30 days poststent implantation is defined as early stent thrombosis. Late-stent thrombosis is defined as stent thrombosis occurring within 30 days and 1 year. Stent thrombosis occurring after >1 year after the index procedure is defined as very late stent thrombosis.

bypass grafting, more multivessel disease, and worse type lesions. They were less likely to be male, currently smoking, and to be treated for acute myocardial infarction. The bypass graft was treated significantly more often, and the stents implanted were on average smaller. No significant differences were observed for the usage of clopidogrel and/or glycoprotein IIb/IIIa inhibitor between the three groups.

Six-Year Clinical Outcome

The 6-year crude event rates stratified according to renal function are shown in Table II for each of the end points. There was a total of 93 deaths (Kaplan–Meier estimate of 34%) in the group with moderate RI, 70 (12%) in the group with mild RI, and 62 (8%) in patients with normal kidney function (normal kidney function vs. mild RI, log-rank P-value = 0.08; normal

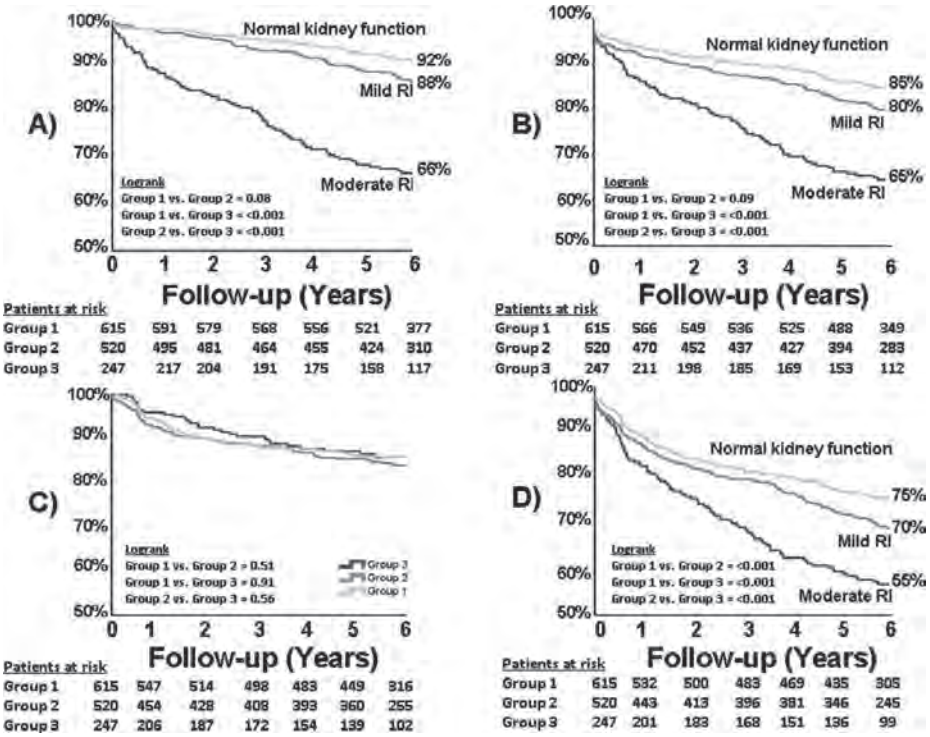

Fig. 1. Cumulative adverse cardiac event free rates of PCI-patients stratified by renal function. A: All-cause mortality curve; (B) all-cause mortality/MI curve; (C) TVR rates at 6-years: Group 1 = 84%, Group 2 = 83%, and Group 3 = 84%; (D) MACE curve.

TABLE III. Six-Year Crude Event Rates Stratified According to Renal Function and Different Stent Types

	Normal kidney function				Mild RI				Moderate RI			
	BMS (n = 175)	SES (n = 208)	PES (n = 232)		BMS (n = 145)	SES (n = 205)	PES (n = 170)		BMS (n = 72)	SES (n = 85)	PES (n = 90)	
Mortality	25 (14.3%)	16 (7.7%)	21 (9.1%)		18 (12.4%)	30 (14.6%)	22 (12.9%)		25 (34.7%)	35 (41.2%)	33 (36.7%)	
Mortality/MI 36 (20.6%)	30 (14.4%)	35 (15.1%)	31 (21.4%)		41 (20.0%)	34 (20.0%)	26 (36.1%)		38 (44.7%)	35 (38.9%)		
MACE	58 (33.1%)	44 (21.2%)	57 (24.6%)		44 (30.3%)	61 (29.8%)	55 (32.4%)		32 (44.4%)	44 (51.8%)	41 (45.6%)	
TVR	33 (18.9%)	24 (11.5%)	34 (14.7%)		22 (15.2%)	33 (16.1%)	27 (15.9%)		13 (18.1%)	11 (12.9%)	8 (8.9%)	
ST	5 (2.9%)	5 (2.4%)	10 (4.3%)	$P = 0.5$	6 (4.1%)	8 (3.9%)	3 (1.8%)	$P = 0.4$	0 (0.0%)	3 (3.5%)	2 (2.2%)	$P = 0.3$
Early	1 (0.6%)	1 (0.5%)	3 (1.3%)	$P = 0.6$	6 (4.1%)	0 (0.0%)	3 (1.8%)	$P = 0.01$	0 (0.0%)	1 (1.2%)	1 (1.1%)	$P = 0.7$
Late	2 (1.1%)	1 (0.5%)	4 (1.7%)	$P = 0.5$	0 (0.0%)	1 (0.5%)	0 (0.0%)	$P = 0.5$	0 (0.0%)	0 (0.0%)	0 (0.0%)	$P = 1.0$
Very late	2 (1.1%)	3 (1.4%)	3 (1.3%)	$P = 1.0$	0 (0.0%)	7 (3.4%)	0 (0.0%)	$P = 0.004$	0 (0.0%)	2 (2.4%)	1 (1.1%)	$P = 0.4$
	SES–BMS	PES–BMS	SES–PES		SES–BMS	PES–BMS	SES–PES		SES–BMS	PES–BMS	SES–PES	
	Multivariate HR (95% CI)				Multivariate HR (95% CI)				Multivariate HR (95% CI)			
Mortality	0.55	0.79	0.94		1.32	0.93	1.34		1.31	1.15	0.98	
	(0.29–1.04)	(0.57–1.10)	(0.66–1.33)		(0.71–2.43)	(0.46–1.89)	(0.75–2.39)		(0.77–2.24)	(0.85–1.55)	(0.75–1.27)	
Mortality/MI	0.70	0.81	1.05		0.96	0.92	1.08		1.28	1.20	0.95	
	(0.43–1.16)	(0.62–1.05)	(0.81–1.35)		(0.60–1.56)	(0.53–1.58)	(0.67–1.74)		(0.76–2.17)	(0.90–1.60)	(0.74–1.23)	
MACE	0.55	0.74	0.95		0.93	1.09	0.99		1.10	1.08	0.98	
	(0.36–0.83)	(0.61–0.91)	(0.78–1.17)		(0.63–1.39)	(0.99–1.03)	(0.68–1.44)		(0.68–1.76)	(0.83–1.39)	(0.78–1.23)	
TVR	0.48	0.75	0.87		0.89	1.08	1.15		0.60	0.65	1.10	
	(0.28–0.84)	(0.57–0.97)	(0.66–1.15)		(0.51–1.56)	(0.59–1.98)	(0.68–1.95)		(0.26–1.39)	(0.41–1.05)	(0.68–1.76)	

BMS, bare-metal stent; CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; TVR, target-vessel revascularization. Stent thrombosis occurring within 30 days poststent implantation is defined as early stent thrombosis. Late stent thrombosis is defined as stent thrombosis occurring within 30 days and 1 year. Stent thrombosis occurring after >1 year after the index procedure is defined as very late stent thrombosis.

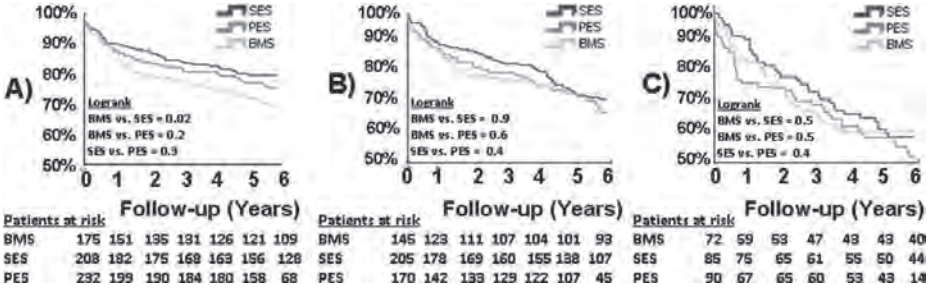

Fig. 2. Cumulative MACE-free rates of PCI-patients stratified by renal function and stent type. A: Group 1: BMS = 70%, SES = 80%, and PES = 76%; (B) Group 2: BMS = 70%, SES = 70%, and PES = 67%; (C) Group 3: BMS = 60%, SES = 58%, and PES = 54%.

kidney function vs. moderate RI, log-rank P-value $<$ 0.001; mild RI vs. moderate RI, log-rank P-value $<$ 0.001). Also, the combined end-point MACE was significantly worse for patients with moderate RI (Fig. 1); however, the efficacy endpoint remained similar between three groups at 6 years. After further stratifying, patients in the three groups according to stent type, the multivariate Cox regression analysis, which was used to correct for baseline differences and (independent) predictors of adverse events, showed that SES and PES decreased the occurrence of TVR and MACE at 6 years in patients with a normal creatinine clearance compared to BMS [adjusted hazard ratio (aHR) = 0.48, 95% CI: 0.28–0.84; aHR = 0.75, 95% CI: 0.57–0.97, respectively]. No differences were noted in safety and efficacy end points between stent types in patients with mild- and moderate renal function (Fig. 2, Table III). More very-late stent thrombosis occurred after SES-implantation in patients with mild renal function compared to PES and BMS ($P = 0.004$).

DISCUSSION

Our main findings show that patients with moderate RI have a worse 6-year survival compared to those with mild RI or normal kidney function. On the contrary, the degree of kidney disease did not significantly affect TVR rates. After adjustment, SES and PES showed a reduction in the occurrence of TVR and MACE in patients with normal kidney function compared to BMS, but not for patients with mild- and moderate RI. In fact, mortality- and TVR rates remained similar for the three stent types in patients with mild- and moderate renal function. Very late stent thrombosis was more common after SES implantation for patients with mild RI.

Cardiovascular disease is the commonest cause of death in CKD patients even after control of the uremic state with dialysis or renal transplantation [16]. This, in addition to the more prevalent risk factors for coronary artery disease including hypertension, diabetes, and dyslipideamia, factors associated with renal disease such as hyperhomocystinaemia, hyperparathyroidism, elevated calcium-phosphate product, fluid overload, uremic toxins, inflammation, and anemia contribute to the extent and severity of the coronary atherosclerosis as well as the higher adverse event rates in this high risk population. The co-existence of these factors in renal dysfunctional state is synergistic. In fact, increased homocysteine and oxidative stress enhance oxidation of low-density lipoprotein, enhancing the latter's atherogenicity [17]. Free apolipoprotein(a) formation is also increased in hyperhomocysteinaemic states, further promoting atherosclerotic plaque formation. Although events such as cardiac death in patients with renal disease can be attributed to causes that are not always directly related with the underlying epicardial artery disease (including microvascular disease, uraemic cardiomyopathy and metabolic derangements), the presence of significant coronary artery stenosis dramatically worsens the prognosis even in the long term.

The appropriate and adequate treatment of epicardial coronary stenosis intuitively prevents cardiac death and other events especially in this subgroup [18]. The choice of safe and effective stent type for revascularisation in CKD patients is therefore highly relevant. Although as we have recently reported, in the general population, SES and PES are more effective in the long term than BMS for the treatment of CAD with some concerns of late stent thrombosis, issues particular to performance of different stent types in CKD patients have not been adequately addressed [19]. The increased restenosis rates after PCI may account in part of the increased mortality of this population.

The "dose-dependent" effect of creatinine (as a measure of renal function) on outcome that we

observed on our study is well documented [20,21]. At large, the differences accompany a worsening disease state of patients, both clinically and angiographically. In fact, patients with worse renal function were older, had more commonly undergone CABG had more multivessel disease and worse type lesions. Unmeasured clinical events such as bleeding, fluid overload, electrolyte imbalances, and dialysis-related complications may also have directly or indirectly contributed to the worse outcome in these patients. Despite reports of increased risk of stent thrombosis with worsening renal function, our data do not support this hypothesis [22–25].

The antirestenotic properties of DES in comparison with BMS were shown to result in clearly superior target vessel revascularization rates in the short term, also for patients with impaired renal function. At 1-year follow-up, patients with renal impairment treated with SES at our institution had significantly less revascularization compared to patients treated with BMS [5]. However, this did not result in a mortality benefit. At 6-years follow-up, however, while SES and PES use had lower revascularisation rates in patients with normal renal function when compared with BMS, there was no difference in this endpoint in patients with mild and moderately impaired renal function. Again, we observed no difference in mortality and myocardial infarctions between stent types used in patients with renal impairment which questions the utility of DES in such patients. This strategy is further jeopardized by the increased incidence of very late ST in patients with SES and the observation of no such events in the BMS group in patients with the worse renal function. It can be hypothesized that the superior efficacy of DES shown in the short term may have been lost by the development of further coronary disease in the nonintervened segments. This would imply that control of the extent and severity of atherosclerosis with renal impairment is probably just as important as stent type use in the long term. Another explanation is that mortality rates were higher in patients with mild–moderate renal insufficiency than in patients with no kidney disease, which could have led to a statistically underpowered difference between both DES and BMS while TVR rates are in fact numerically higher.

The present study is based on a registry data from a single center and carries inherent limitations as such. Although the three stent types were exclusively used in their specific time period as previously described for our RESEARCH and TSEARCH registries, unmeasured differences other than stent type would not be adjusted for. Creatinine clearance was not available in 10%; however, we have no reason to suspect that this could favor any group or stent type.

Renal impairment is associated with a worse 6-year survival in patients undergoing revascularization with coronary stents. However, revascularization rates in our study were not influenced by the presence or degree of renal dysfunction in the long term. With respect to the choice of stent type, in the long term, DES use seems to loose the advantage over BMS in patients with renal impairment as opposed to patients with normal kidney function.

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APPENDIX

The following operators were involved in the procedures of the discussed patient populations: Chourmouzios A. Arampatzis, MD, Eugene McFadden, MD, PhD, Pim J. de Feyter, MD, PhD, Willem J. van der Giessen, MD, PhD, Sjoerd H. Hofma, MD, PhD, Angela Hoye, MBChB, MRCP, Peter P.T. de Jaegere, MD, PhD, Patrick W. Serruys, MD, PhD, Evelyn Regar, MD, PhD, Georgios Sianos, MD, PhD, and Pieter C. Smits, MD, PhD.

Part V

PERCUTANEOUS REVASCULARIZATION IN ACUTE CORONARY SYNDROMES

5.1

Acute coronary syndromes: No-reflow--an ominous sign of cardiac dysfunction.

Magro M, Serruys PW.

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diseased tooth often migrate to the blood stream (bacteremia). Periodontal bacteria have been identified in atheromas and could provide the inflammatory stimulus leading to atheroma formation.[9] In addition, studies of animal models, for example a study in rabbits by Jain and colleagues,[10] have demonstrated that atheroma formation is increased in animals with periodontitis, which suggests a potential causal role for periodontal infection in CVD.

> “...inflammatory cytokines induced by periodontitis could mediate the link with CVD...”

The risk factors shared between periodontitis and CVD present the possibility that the association between the two conditions is, at least in part, the expression of two unrelated inflammatory diseases in a susceptible individual. Type 2 diabetes mellitus, cigarette smoking, obesity, lipid alterations, hypertension, physical inactivity, family history of CVD and periodontal disease, advancing age, and male sex are all risk factors for CVD and are commonly found in patients with periodontitis (Figure 1).

On the strength of the current evidence for an association between CVD and periodontitis, a series of clinical recommendations were made in the aforementioned consensus report.[6] Patients with periodontitis who have two or more known risk factors for atherosclerosis should be referred by the dental team for evaluation of atherosclerotic risk, which should include physical examination and annual measurement of blood pressure and blood lipid profile. Patients with periodontitis and abnormal serum lipid values, elevated levels of plasma CRP (as measured by the high-sensitivity CRP test), or both are recommended to follow a multifaceted lifestyle modification program to reduce CVD risk. Cessation of cigarette smoking is recommended for all patients with periodontitis. Furthermore, all patients with periodontitis who have elevated blood pressure (>140/90 mmHg) should be treated according to standard hypertension management protocols and should undertake lifestyle changes, including reduction of weight and dietary sodium intake, as appropriate. Periodontal evaluation should be considered in patients with CVD who have signs or symptoms of gingival disease or unexplained tooth loss. Moreover, when periodontitis is newly diagnosed in patients with CVD, dentists and physicians should closely collaborate to optimize CVD risk reduction and periodontal care.

Although the association between CVD and periodontitis and the biologically plausible pathways underlying this link are reasonably well understood, we still need randomized, controlled intervention trials to firmly establish if, and the extent to which, prevention or resolution of periodontal inflammation will decrease the risk of primary or secondary CVD events. On the basis of our current knowledge, however, cardiologists and other physicians who manage patients with CVD should collaborate with dentists to moderate cardiovascular risk in patients who also suffer from periodontitis.

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ACUTE CORONARY SYNDROMES

No-reflow—an ominous sign of cardiac dysfunction

Michael Magro and Patrick W. Serruys

Mechanical reperfusion in acute myocardial infarction does not always result in desirable optimal microvascular perfusion. Failure to achieve a normal myocardial blush in the infarcted region by contrast injection immediately after percutaneous coronary intervention—the 'no-reflow' phenomenon—is an ominous sign whose prognostic importance may go beyond its intimate association with infarct size.

Primary percutaneous coronary intervention (PPCI) can restore epicardial coronary flow in the majority of patients presenting with an acute ST-segment elevation myocardial infarction (STEMI). However, achievement of normal or near-normal flow in the epicardial artery does not guarantee restitution of microvascular perfusion or limitation of infarct size. The no-reflow phenomenon—an angiographic demonstration of failure of restoration of microvascular perfusion after intervention—and its negative impact have been studied by Ndrepepa *et al.*[1] The investigators showed that no-reflow strongly predicted 5-year mortality, independent of infarct size, in patients with STEMI.

In this study, 1,406 patients treated with PPCI within 24 h of the onset of symptoms of STEMI underwent ^{99m}Tc-sestamibi single-photon emission CT (SPECT), to determine the size of the infarct, 7–14 days after reperfusion therapy and were clinically followed

for up to 5 years. The no-reflow phenomenon was identified in 410 patients (29%). Diagnostic criteria included angiographic evidence of reopening of an occluded coronary artery and successful stent placement with no evidence of flow-limiting residual stenosis (<50%), dissection, spasm or apparent thrombus, together with angiographic documentation of a Thrombolysis In Myocardial Infarction (TIMI) flow grade ≤2, or a TIMI flow grade 3 with a TIMI myocardial perfusion grade (TMPG) 0 or 1, at least 10 min after the end of PPCI.[1]

> "The presence of no-reflow could ... identify patients with generalized microvascular dysfunction"

Interestingly no-reflow was significantly more common among patients who had clinical factors associated with worse prognosis after acute myocardial infarction. Specifically, individuals with no-reflow were older (median age: 65.3 years versus 61.3 years, $P<0.001$), more commonly had previous CABG surgery (5.4% versus 2.5%, $P=0.007$), had a higher Killip class at presentation (class III–IV: 10.5% versus 8.4%) and, importantly, had a longer ischemic time (median time: 5 h versus 4 h, $P<0.001$),[1] which is a major determinant of infarct size, than patients without no-reflow. Patients in the no-reflow group also had a lower left ventricular ejection fraction (median: 48% versus 50%, $P<0.001$), more commonly presented with multivessel disease (69.0% versus 63.5%, $P=0.046$), and more-commonly had saphenous vein graft intervention (3.9% versus 0.8%, $P<0.001$).[1] Patients with no-reflow were also more likely than those without no-reflow to present with a closed infarct related artery, with 73.4% of patients having TIMI flow grade 0 or 1 at presentation as opposed to 52.9% with TIMI flow grade 2 or 3. Furthermore, levels of peak cardiac enzymes were higher in these patients (median peak troponin: 4.9 µg/l versus 3.5 µg/l, $P<0.001$; median peak creatine kinase MB: 157.5 U/l versus 123.5 U/l, $P<0.001$).[1]

Infarct size, as estimated by SPECT, was larger in the no-reflow group (percentage of the left ventricle affected: 15% versus 8%, $P<0.001$), which was associated with higher mortality at 5 years, than among patients in whom restoration of blood flow was achieved (12.4% versus 6.3%; odds ratio 2.18, 95% CI 1.46–3.27, $P<0.001$). On multivariable analysis, in a model that included infarct size, the no-reflow phenomenon was an independent predictor of 5-year mortality (adjusted hazard ratio 1.66, 95% CI 1.17–2.36, $P=0.004$). Furthermore, no-reflow increased the risk of mortality in all three tertiles of patients stratified according to their infarct sizes.[1]

The relationship between angiographically determined no-reflow and infarct size is more complex than previously perceived, a fact that is highlighted by the Ndrepepa *et al.* study.[1] The no-reflow phenomenon is reversible in some cases, and these patients have smaller infarct sizes, less left ventricular remodeling, and a better prognosis than patients who have persistent no-reflow.[2] Angiographically defined no-reflow, therefore, includes a 'benign' subgroup, which should weaken the prognostic power of this phenomenon if no-reflow is determined solely by infarct size. Instead, the study by Ndrepepa *et al.* infers that no-reflow has prognostic implications beyond its association with infarct size. This finding is consistent with the results of earlier studies in which ST-segment resolution, TIMI flow grade, myocardial contrast echocardiography, and MRI were used to measure microvascular obstruction.[2–4] The degree of microvascular dysfunction—and, therefore, the likelihood of the no-reflow phenomenon—in the first 24 h of the myocardial infarction could be correlated with the size of a myocardial area at risk, which is often larger than the subsequently regressed infarct area measured 7 days following the acute event.

The presence of no-reflow could also identify patients with generalized microvascular dysfunction, such as those with hypercholesterolemia, hyperglycemia, or the metabolic syndrome, who are more likely to experience future adverse cardiac events irrespective of the infarct size at the index event. The mechanisms by which poor perfusion is achieved in these patients are not clear, but may include enhanced prothrombotic and proinflammatory states, and poor endothelial function from oxidative stress and reduced nitric oxide concentration. In this context, adequate glycemic control and statin therapy have been associated with a decreased incidence of no-reflow.[5] Further knowledge of the pathophysiology and significance of the no-reflow phenomenon is essential to enable the development of interventions that could mitigate the adverse clinical course in these patients.

Preventing a large infarct is undoubtedly the most effective way of reducing the incidence of no-reflow. Therefore, measures to decrease ischemic time are crucial—educating patients to seek early medical attention, prompt transport to a PPCI center, and minimizing door-to-balloon times remain pivotal steps that need regular audit and improvement. An MRI study showed a marked increase in the infarct size, from 8% of the left ventricle in patients reperfused within 90 min of symptom onset to 11.7%, 12.7%, and 17.9% in those reperfused between 90 and 150 min, 150–360 min, and >360 min, respectively.[4] Microvascular obstruction increased with longer ischemic times (0.5%, 1.5%, 3.7%, and 6.6% respectively, P for trend = 0.047).[4] Prehospital administration of antiplatelet agents and heparin is more likely to result in patency of the infarct-related artery on arrival at the catheterization laboratory, and is inherently associated with lower infarct size secondary to earlier 'spontaneous' reperfusion, lower incidence of no-reflow, and better prognosis.[6]

Embolization of atherothrombotic debris through occlusion of prearterioles is an established cause of myocardial injury, particularly with larger particles (>200 µm in diameter), and is one possible mechanism of the no-reflow phenomenon. A high thrombus burden is more likely to result in distal embolization and is an independent predictor of mortality; in fact, thrombus aspiration has been shown to markedly improve myocardial perfusion and to reduce mortality.[7] The benefit of the glycoprotein IIb/IIIa inhibitor abciximab in this situation is also likely to be mediated by its effect on platelet inhibition and thrombus or microthrombus limitation, although other mechanisms, including its effects on endothelial function and leukocyte adhesion to the endothelium, have also been postulated.[8]

In addition to clogging, microvascular dysfunction can be caused by the effects of ischemic injury and reperfusion injury of the myocardium. Increased myocardial wall thickness resulting from tissue edema can increase intramyocardial pressures and lead to mechanical no-reflow. The area at risk is determined by the extent of myocardium subtended by the infarct-related artery, which in turn is associated with no-reflow.[9] On a microvascular level, ischemic endothelial cells exhibit protrusions and membrane-bound bodies that can cause capillary luminal obliteration, while myocardial cell swelling and interstitial edema cause microvascular compression.[10]

In-depth analysis of the relationship between no-reflow and infarct size was

limited in the study by Ndrepepa *et al.*[1] The use of pharmacological or mechanical measures in the no-reflow group was not reported, and could have led to underestimation of the difference in outcome between patients with and without no-reflow. Patients with cardiogenic shock, and those with cardiac arrest who survived beyond the SPECT study, were not specifically excluded. Whether, and to what extent, these strongly prognostic TIMI risk variables would have affected the hazard ratios in the multivariable model remains unexplored. Unfortunately, details of management at follow-up were not provided. Differences in completeness of revascularization or in medical treatment at follow-up between the no-reflow group and the controls might also have influenced long-term survival. Nonetheless, any novel interventions that aim to improve prognosis in patients with acute myocardial infarction should be able to demonstrate a reduction in the incidence of the no-reflow phenomenon.

In conclusion, no-reflow in acute myocardial infarction reflects substantial microvascular cardiac dysfunction and is a strong predictor of mortality. The severity of microvascular dysfunction is determined both by the extent of myocardial cell death and by other diverse pathophysiological mechanisms, which are still poorly understood. Further research that aims to clarify the role of these mechanisms is essential in order to tailor appropriate and effective therapeutic strategies.

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CORONARY ARTERY DISEASE

Percent stenosis in CAD—a flaw in current practice

K. Lance Gould and Nils P. Johnson

The optimum strategy to treat patients with coronary artery disease (CAD) has been under debate. New data show that revascularization guided by fractional flow measurements leads to better outcomes than revascularization guided by arteriography. We call for a paradigm shift in CAD care, with coronary flow measurements by PET as key to diagnosis and clinical decision-making.

The 2-year follow-up data from the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial[1] show that patients with coronary artery disease (CAD) undergoing revascularization guided by pressure-wire measurements of fractional flow reserve (FFR) to indicate potential ischemia had significantly fewer adverse outcomes and better event-free survival than patients undergoing revascularization based on arteriographic percent stenosis without FFR measurements. These results confirm the original report from the FAME study.[2]

Randomized trials comparing revascularization procedures with medical treatment in patients with stenosis of comparable severity, as determined by coronary arteriography, show no reduction in the incidence of adverse events with revascularization.[3] The common explanation for failure of revascularization to improve event-free survival over medical treatment is progression of atherosclerosis and plaque rupture despite revascularization of localized stenosis. However, in some trials, patients who underwent revascularization also received reasonably good medical and lipid-lowering treatment with no difference in outcomes.[3] Paradoxically, in the randomized FAME trial, revascularization based on coronary flow reserve capacity, as measured by FFR, significantly reduced coronary events and was associated with better event-free survival than revascularization based on arteriographic percent stenosis alone.[1,2]

> “...PET ... enables quantification of the functional severity of diffuse and segmental CAD”

The answer to this paradox appears shockingly simple and reveals the profound flaw in the universal use of percent stenosis to evaluate the severity of CAD and deciding on revascularization procedures.[4] Revascularization in trials that compared this treatment with medical therapy was performed on the basis of arteriographic percent stenosis. However, percent stenosis is poorly related to FFR or coronary flow reserve capacity.[4–8] In patients with visually estimated 50–70% diameter stenosis on coronary arteriograms, only 35% had FFR indicating potential ischemia.[8] In patients with visually estimated 71–90% diameter stenosis on coronary arteriograms, 20% had FFR indicating no substantial ischemia, whereas 80% had FFR justifying revascularization.[8] These data confirm that coronary arteriography is not adequate for assessing the functional or flow reserve capacity

5.2

Prognostic Value of Infarct Size and Microvascular Obstruction Measured by Cardiac Magnetic Resonance in Patients with ST-Segment Elevation Myocardial Infarction. A Meta-Analysis of Individual Patient Data.

Van Kranenburg M, Magro M, de Waha S, Thiele H, Bodi Peris V, Cochet A, Klug G, Wu E, Atar D, Bernhardt P, Delewi R, Boersma E, Zijlstra F, van Geuns RJ.

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Prognostic Value of Microvascular Obstruction and Infarct Size, as Measured by CMR in STEMI Patients

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ABSTRACT

The aim of this study was to evaluate the value of microvascular obstruction (MO) and infarct size as a percentage of left ventricular mass (IS%LV), as measured by contrast-enhanced cardiac magnetic resonance, in predicting major cardiovascular adverse events (MACE) at 2 years in patients with ST-segment elevation myocardial infarction reperfused by primary percutaneous coronary intervention. Individual data from 1,025 patients were entered into the pooled analysis. MO was associated with the occurrence of MACE, defined as a composite of cardiac death, congestive heart failure, and myocardial re-infarction (adjusted hazard ratio: 3.74; 95% confidence interval: 2.21 to 6.34). IS% LV ≥25% was not associated with MACE (adjusted hazard ratio: 0.90; 95% confidence interval: 0.59 to 1.37). The authors conclude that MO is an independent predictor of MACE and cardiac death, whereas IS%LV is not independently associated with MACE. (J Am Coll Cardiol Img 2014;7:930–9) © 2014 by the American College of Cardiology Foundation.

In the setting of ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (pPCI) is the preferred reperfusion strategy and a cornerstone in the treatment of patients with STEMI (1). A substantial proportion of STEMI patients display a "no-reflow" phenomenon despite successful epicardial reperfusion (2). This phenomenon is characterized by either absent

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or inadequate myocardial tissue reperfusion despite successful reopening of the infarct-related artery (3).

No-reflow is thought to be a consequence of microvascular obstruction (MO), caused by numerous components, including distal atherothrombotic embolization, ischemic injury, reperfusion injury, and susceptibility of the coronary microcirculation to injury (2). No-reflow can be assessed with cine coronary angiography, ST-segment resolution measured on electrocardiography, and noninvasive imaging techniques such as myocardial contrast echocardiography and contrast-enhanced cardiac magnetic resonance (CE-CMR).

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In patients with STEMI, the presence and magnitude of MO are visualized by CE-CMR, with accurate and reproducible measurements of left ventricular ejection fraction (LVEF) and infarct size (IS) (4). Compared with myocardial segments without MO, segments with MO are more likely to demonstrate wall thinning and are less likely to demonstrate improvement of segmental wall thickening during follow-up study (5). Moreover, MO is an important predictor of global functional recovery after STEMI (6). Several studies suggest that MO is associated with worse prognosis (7-13). However, previous studies in this regard have been hampered by a limited number of patients, evaluated a combined clinical endpoint, and were single-center studies (7-13). Furthermore, although intuitively IS measured within 2 weeks after STEMI is an important independent determinant of outcome, there is conflicting evidence to support its independent predictive value for major adverse cardiac events (MACE) (9,12,14).

We performed a meta-analysis of individual patient data to evaluate the hypotheses that MO and IS expressed as a percentage of left ventricular (LV) mass (IS%LV) are independent predictors of MACE and cardiac death in patients with STEMI undergoing pPCI.

METHODS

STUDY SELECTION. The MEDLINE database was searched for citations of in-human studies published in English from January 2004 to April 2012, using the following terms: microcirculation(MESH), magnetic resonance imaging, myocardial infarction, and microvascular obstruction. A total of 134 publications were identified. Related studies from the reference lists of retrieved papers, and the bibliographies of the coauthors, were included. Observational studies in STEMI patients who underwent pPCI within 12 h of symptom onset, followed by CE-CMR within 14 days, were eligible for inclusion. Studies in >60 patients were invited to participate. In the case of experimental studies, data from only the placebo groups were included in the analysis.

DATA COLLECTION. Requested variables consisting of baseline characteristics, variables used in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) risk score (15), the Zwolle primary PCI index (16), and the Thrombolysis in Myocardial Infarction (TIMI) risk score (17); baseline CE-CMR variables; and clinical outcomes (MACE) were mentioned beforehand in a protocol, along with study rationale and study design. The protocol was sent to participating centers. Previous approval of the individual study design by a local ethics committee was necessary for participation. Datasets from participating centers were merged by the coordinating center (Erasmus Medical Center, Rotterdam, the Netherlands). Queries were sent to the primary investigators in cases in which further data and clarification were needed.

DEFINITIONS/CE-CMR. *STEMI* was defined on the basis of the definitions used by the authors of the primary publications (8-13,18,19). All clinical and angiographic variables were study based. Angiographic left main coronary artery lesions were categorized as left anterior descending artery lesions. Imaging was performed in different centers on 1.5-T scanners from different vendors (Online Table 1). The scanning protocols, CE-CMR parameters, and data analysis have been described in the included studies (8-13,18,19). All investigators but one used a steady-state, free-precession sequence for cine CMR (Online Table 1). LV end-diastolic volume, LV end-systolic volume, and LVEF were short-axis based, as provided by the investigators. If LV end-diastolic and end-systolic volume were not indexed, the Mosteller equation was used to adjust these for body surface area. Late gadolinium enhancement was performed by the different centers by use of a (phase-sensitive) inversion recovery gradient echo sequence. *MO,* as visualized with late gadolinium enhancement, was defined as any region of hypoenhancement within the hyperenhanced area. IS was determined on short-axis images. IS was expressed

ABBREVIATIONS AND ACRONYMS

CE-CMR = contrast-enhanced cardiac magnetic resonance

IS = infarct size

LV = left ventricular

MACE = major adverse cardiac events

MO = microvascular obstruction

pPCI = primary percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

both in grams and as a percentage of the LV mass (IS%LV). IS%LV was determined by manual or automated tracing of the infarct border. In patients with MO, regions of hypoenhancement were included in the IS. In 2 studies, patients with prior infarction were included (8,12). In patients with prior myocardial infarction, only the region indicative of acute infarction (8), corresponding with edema in T_2-weighted imaging (12), was measured in delayed-enhancement images.

ENDPOINTS. The primary endpoint was the prevalence of *major adverse cardiovascular events* (MACE), defined as a composite of cardiac death, myocardial re-infarction, and new congestive heart failure, at 2 years. The secondary endpoint was cardiac mortality. *Congestive heart failure* was defined as any symptom of cardiac decompensation requiring hospitalization. The individual study investigators provided previously defined and used events (Online Table 1). If a patient experienced more than one event, the first event was chosen for the combined clinical endpoint. Patients were considered at risk from the time of admission for the treatment of STEMI.

STATISTICAL ANALYSIS. Continuous data with normal distribution are presented as mean ± SD. Non-normally distributed variables are reported as median with corresponding interquartile range (IQR). Categorical variables are represented by frequencies and percentages. Patients were categorized according to the presence of MACE. Differences in continuous variables between categories of patients were studied by the unpaired Student *t* test or the Mann-Whitney *U* test (in cases of non-normal distribution). Proportions were compared using the chi-square test or the Fisher exact test, where applicable. The incidences of the primary and secondary endpoints are reported as Kaplan-Meier estimates at a follow-up of 2 years. As small infarcts and minor decreases in LVEF might not have an impact on outcome, the relationship between these variables on outcome was investigated by plotting IS%LV and LVEF against event-free survival. A log-rank test was used to evaluate differences in freedom from study endpoints between categories of patients. Univariate and multivariate Cox regression analyses, stratified by study, were used to determine the prognostic value of MO, IS%LV, and LVEF with respect to the primary and secondary endpoints. Predictors of cardiac death and MACE in published reports—namely, age (>65 years); sex (female); the presence of diabetes, hypertension, anterior myocardial infarction (culprit lesion in the left anterior descending artery), or multivessel disease; TIMI flow grade after PCI (reference: TIMI flow grade after PCI of 0 or 1); and CMR-based LVEF (12,16,17)—were entered into the univariate regression model, along with MO, IS%LV, LV end-diastolic volume index, and LV end-systolic volume index (9). Variables that resulted in a p value of <0.10 in the univariate Cox model were entered into the multivariate Cox proportional hazards model, with respect to multicollinearity. LV end-systolic volume index was not entered into the multivariate model due to a collinear relation with LVEF (Pearson correlation: -0.774). We applied the method of backward selection; all variables with a p value of <0.05 remained. The proportional hazards assumption was validated graphically. In cases of missing data (the requested variable data were unavailable in >5.0% of the cohort), these variables were not taken into account in the regression analysis (e.g., time to reperfusion and Killip class). We report unadjusted hazard ratios (HRs) and adjusted hazard ratios (aHRs), 95% confidence intervals (CIs), and p values. We determined the *c*-index (20) to report on the performance of the models to discriminate between patients with and without the study endpoints. The incremental value of IS%LV, LVEF, and MO was compared with that from a model with established clinical variables. *c*-Index models were developed on the basis of multivariate Cox models. We applied, for these models, a backward variable-selection method; all

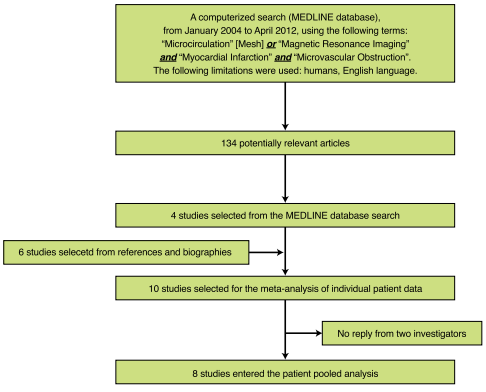

FIGURE 1 Computerized Search

A computerized literature search of citations was performed.

variables with a p value of <0.05 remained. Two-sided probability values with an α level of ≤0.05 were considered to be statistically significant. Statistical analysis was performed using the statistical packages IBM SPSS Statistics version 20.0.01 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). Kaplan-Meier curves were drawn with GraphPad Prism version 4.00 (GraphPad Software Inc., San Diego, California).

RESULTS

PATIENT CHARACTERISTICS. We identified 10 eligible observational and experimental studies. The principal investigators of these studies were invited to participate in this collaborative analysis. Eight of 10 investigators provided individual patient data (**Figure 1**). In this pooled analysis, 2 studies with 193 potentially eligible patients were not included due to investigator unresponsiveness (14,21).

The individual study characteristics are summarized in Online Table 1. The inclusion procedure is shown in **Figure 2**. Of 1,488 AMI patients, 150 patients (10.1%) were unable to have a CMR examination, and 313 patients were excluded due to other reasons (**Figure 2**). Consequently, data from 1,025 STEMI patients who underwent reperfusion by pPCI between April 9, 1999 and September 28, 2008 were included in the patient pooled analysis. The mean age at inclusion was 59.7 ± 12.7 years, and 77.7% of the cohort were men (n = 796). The median time to reperfusion was 3.3 h (IQR: 2.1 to 4.9 h). CE-CMR was performed within a median of 4 days (IQR: 2 to 6 days) after the occurrence of STEMI. MO was present in 56.3% of patients in the overall cohort. Of patients with TIMI flow grade after PCI of 3 (927 of 1,019 [91.0%]), MO was present in 54.9%. The mean LVEF was 48.0 ± 12.3%. Of the entire cohort, 14.7% had a severely depressed (<35%) LVEF. The baseline characteristics of patients with MACE and patients without MACE are compared in **Table 1**. The median duration of available follow-up was 12 months (IQR: 4 to 21 months).

PREDICTORS OF MACE. The composite endpoint occurred in 130 patients within 2 years of follow-up. In 9 patients, an event occurred between the index event and the CE-CMR study. Cardiac death occurred in 25 patients; myocardial re-infarction, in 47 patients; and congestive heart failure, in 58 patients. The Kaplan-Meier estimate of freedom from MACE at 2 years was 76.5% in patients with MO versus 93.0% in patients without MO (p < 0.001).

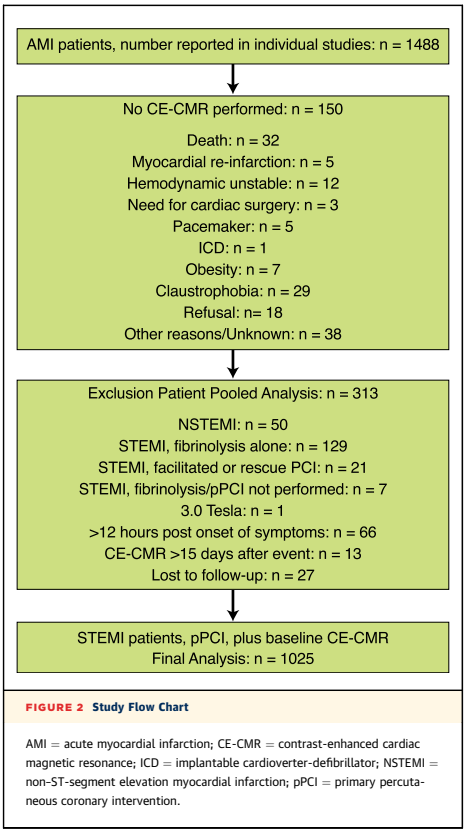

FIGURE 2 Study Flow Chart

AMI = acute myocardial infarction; CE-CMR = contrast-enhanced cardiac magnetic resonance; ICD = implantable cardioverter-defibrillator; NSTEMI = non-ST-segment elevation myocardial infarction; pPCI = primary percutaneous coronary intervention.

For both LVEF and IS%LV, nonlinear relationships were observed (**Figures 3 and 4**). Therefore, these 2 variables were categorized using tertiles, which provides a large number of events per category while respecting nonlinearity. For LVEF, the first tertile (cutoff: 42.7%, simplified to ≤40%, used in the CADILLAC risk score [15]) was compared to the reference group (LVEF >40%). For IS%LV, the last tertile (cutoff: 24.7%, simplified to ≥25%) was compared to the reference group (IS%LV <25%). The Kaplan-Meier estimate of freedom from MACE at 2 years was 74.3% in patients with IS%LV ≥25% versus 87.4% in patients with IS%LV <25% (p < 0.001). Kaplan-Meier curves for MACE by MO and IS%LV in the entire cohort, and grouped by MO and

TABLE 1 Patient Characteristics

	Entire Cohort (n = 1,025)	MACE (n = 130)	No MACE (n = 895)	p Value
Demographics				
Age, yrs	59.7 ± 12.7	61.8 ± 13.3	59.4 ± 12.6	0.04
Male	796 (77.7)	94 (72.3)	702 (78.4)	0.12
BMI, kg/m^{2*}	27.0 ± 3.8	27.2 ± 4.1	27.0 ± 3.7	0.60
CV risk factors				
Hypertension	530/1,012 (52.4)	70/128 (54.7)	460/884 (52.0)	0.58
Hypercholesterolemia	380/1,010 (37.6)	57/128 (44.5)	323/882 (36.6)	0.08
Current or prior smoking	507/1,023 (49.6)	54/130 (41.5)	455/893 (51.0)	0.02
Family history of MI†	278/937 (29.7)	37/121 (30.6)	241/816 (29.5)	0.81
Diabetes	176/1,012 (17.4)	35/128 (27.3)	141/884 (16.0)	<0.001
Prior MI‡	47/948 (5.0)	12/123 (9.8)	35/825 (4.2)	0.009
Prior CABG§	10/947 (1.1)	2/123 (1.6)	8/824 (1.0)	0.51
Angiographic variables				
Time to reperfusion	3.3 (2.1-4.9)	3.5 (2.1-4.9)	3.2 (2.1-4.9)	0.57
Infarct-related artery				
LAD	514/1,023 (50.2)	73/128 (57.0)	441/895 (49.3)	0.10
RCA	413/1,023 (40.4)	43/128 (33.6)	370/895 (41.3)	0.10
LCA	96/1,023 (9.4)	12/128 (9.4)	84/895 (9.4)	0.99
N-vessel disease				
1	563/1,004 (56.1)	53/126 (42.1)	510/878 (58.1)	<0.001
2	280/1,004 (27.9)	39/126 (31.0)	241/878 (27.4)	0.41
3	161/1,004 (16.0)	34/126 (27.0)	127/878 (14.5)	<0.001
Multivessel disease	441/1,013 (43.5)	73/127 (57.5)	368/886 (41.5)	<0.001
TIMI flow grade after PCI				
0	14/1,019 (1.4)	6/129 (4.7)	8/890 (0.9)	<0.001
1	14/1,019 (1.4)	5/129 (3.9)	9/890 (1.0)	0.009
2	64/1,019 (6.3)	9/129 (7.0)	55/890 (6.2)	0.73
3	927/1,019 (91.0)	109/129 (84.5)	818/890 (91.9)	0.006
Enzymatic IS				
Maximal CK‖	2,161 (1,040-4,160)	2,729 (1,169-6,024)	2,109 (1,031-3,913)	0.04
CE-CMR variables				
Time from MI to CE-CMR, days¶	4 (2-6)	4 (2-6)	4 (2-6)	0.57
Presence of MO	577 (56.3)	109 (83.8)	468 (52.3)	<0.001
IS, %LV#	18.5 (9.2-28.3)	24.9 (14.4-37.4)	18.0 (8.9-26.7)	<0.001
IS, g	22.3 (10.8-37.4)	33.7 (15.3-54.1)	21.0 (10.2-34.7)	<0.001
LVEF, %	48.0 ± 12.3	41.4 ± 13.3	48.9 ± 11.9	<0.001
LVESV, ml	80.5 ± 35.7	94.7 ± 42.0	78.4 ± 34.2	<0.001
LVESV index, ml/m^2	41.3 ± 17.2	48.4 ± 19.6	40.3 ± 16.6	<0.001
LVEDV, ml	150.5 ± 42.4	156.3 ± 45.3	149.6 ± 41.9	0.09
LVEDV index, ml/m^2	77.4 ± 19.6	80.5 ± 20.9	77.0 ± 19.4	0.05

Values are mean ± SD, n (%), n/N (%), or median (IQR). Data missing in the following number of cases: *124 (12.1%), †88 (8.6%), ‡77 (7.5%), §78 (7.6%), ‖278 (27.1%), and ¶446 (43.5%) (reperfusion within 12 h). #Data missing in >7.5% of the cohort.

BMI = body mass index; CABG = coronary artery bypass grafting; CE-CMR = contrast-enhanced cardiac magnetic resonance; CK = creatine kinase; CV = cardiovascular; IQR = interquartile range; IS = infarct size; LAD = left anterior descending; LCA = left circumflex artery; %LV = percentage of LV mass; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; MO = microvascular obstruction; PCI = percutaneous intervention; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

IS%LV, are depicted in **Figures 5 to 7**. The Kaplan-Meier estimate of freedom from MACE was 71.3% in patients with IS%LV ≥25% with MO versus 94.9% in patients with IS%LV <25% without MO ($p < 0.001$).

Univariate Cox regression is summarized in **Table 2**. MO (HR: 4.68; 95% CI: 2.86 to 7.66), IS%LV ≥25% (HR: 2.04; 95% CI: 1.42 to 2.92), and LVEF ≤40% (HR: 3.45; 95% CI: 2.40 to 4.97) were associated with MACE on univariate Cox regression analysis. Sex (HR: 1.34; 95% CI: 0.89 to 2.00) and anterior myocardial infarction (HR: 1.30; 95% CI: 0.90 to 1.87) were not associated with MACE on univariate Cox regression analysis.

Multivariate Cox regression is summarized in **Table 3**. MO (aHR: 3.74; 95% CI: 2.21 to 6.34) and

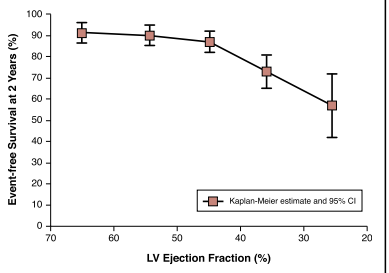

FIGURE 3 Relationship Between LV Ejection Fraction and Event-Free Survival

Values are Kaplan-Meier estimates (95% confidence interval), by LV ejection fraction category (>60%, 50% to ≤60%, 40 to ≤50%, 30% to ≤40%, or <30%). LV = left ventricular.

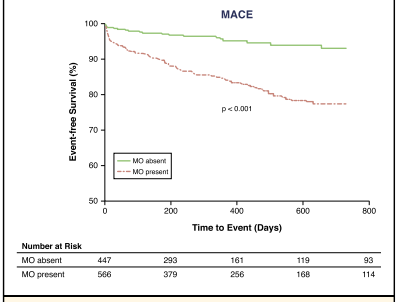

FIGURE 5 Relationship Between MO and Event-Free Survival

Values are Kaplan-Meier estimates in patients with microvascular obstruction (MO) versus patients without MO, indicating the time to major adverse cardiovascular events (MACE), follow-up 2 years.

LVEF ≤40% (aHR: 2.30; 95% CI: 1.48 to 3.58) were associated with MACE, whereas IS%LV ≥25% and diabetes were not independently associated with MACE (model I). After the application of the backward variable-selection method, five variables (age, multivessel disease, TIMI flow grade after PCI, MO, and LVEF ≤40%) remained significant (model II). In a separate analysis, IS%LV, unadjusted for MO and LVEF, but adjusted for age, multivessel disease, and TIMI flow grade after PCI, was associated with the occurrence of MACE (aHR: 1.82; 95% CI: 1.26 to 2.63) (data not shown).

The addition of IS%LV ≥25% to a model with age, multivessel disease, and TIMI flow grade after PCI (model a) resulted in an increase of the *c*-index from 0.59 to 0.61 (model b) in the prediction of MACE. The addition of LVEF ≤40% resulted in an increase from 0.59 to 0.66 (model c), with a further increase to 0.70 (model e) when MO was added (**Table 4**).

PREDICTORS OF CARDIAC DEATH. The Kaplan-Meier estimate of freedom from cardiac death at 2 years was 96.7% (MO vs. no MO: 99.8% vs. 94.6%;

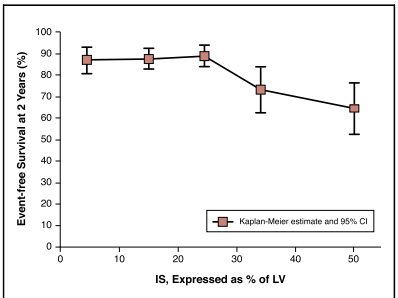

FIGURE 4 Relationship Between IS%LV and Event-Free Survival

Values are Kaplan-Meier estimates (95% confidence interval), by IS%LV category (0 to ≤10%, 10% to ≤20%, 20% to ≤30%, 30 to ≤40%, or >40%). IS%LV = infarct size expressed as a percentage of left ventricular mass.

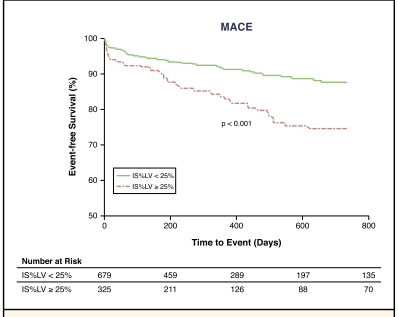

FIGURE 6 Relationship Between IS%LV and Event-Free Survival

Values are Kaplan-Meier estimates in patients with IS%LV ≥25% versus <25%, indicating the time to MACE, follow-up 2 years. Abbreviations as in **Figures 4 and 5**.

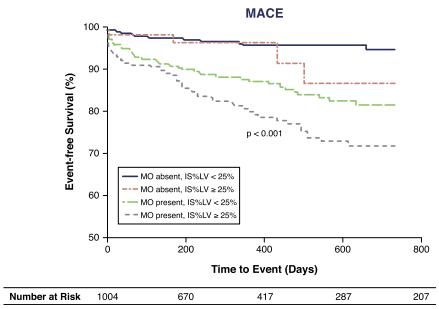

FIGURE 7 Relationship Between MO and IS%LV and Event-Free Survival

Values are Kaplan-Meier estimates in patients with IS%LV ≥25% versus <25%, grouped by the presence or absence of MO, indicating the time to MACE, follow-up 2 years. Abbreviations as in **Figures 4 and 5**.

TABLE 3 Association of Patient Characteristics With MACE at 2 Years: Multivariate Cox Regression Analysis

	aHR	95% CI	p Value
Model I*			
Age	1.54	1.04–2.27	0.03
Diabetes	1.25	0.80–1.94	0.33
Multivessel disease	1.56	1.07–2.28	0.02
TIMI flow grade after PCI	2.11	1.04–4.27	0.04
Presence of MO	3.74	2.21–6.34	<0.001
IS%LV ≥25%	0.90	0.59–1.37	0.63
LVEF ≤40%	2.30	1.48–3.58	<0.001
LVEDV index	1.00	0.99–1.01	0.58
Model II†			
Age	1.58	1.08–2.30	0.02
Multivessel disease	1.56	1.08–2.27	0.02
TIMI flow grade after PCI	2.25	1.14–4.45	0.02
Presence of MO	3.72	2.22–6.25	<0.001
LVEF ≤40%	2.40	1.63–3.53	<0.001

*Before backward variable selection in 970 patients, 118 events. †Backward variable selection in 984 patients, 118 events.

aHR = adjusted hazard ratios; other abbreviations as in **Tables 1 and 2**.

p < 0.001). The Kaplan-Meier estimate of freedom from cardiac death at 2 years was 95.2% in patients with IS%LV ≥25% versus 97.3% in patients with IS% LV <25% (p < 0.21) (data not shown).

Univariate Cox regression is summarized in **Table 5**. MO (HR: 15.02; 95% CI: 2.01 to 112.24) and LVEF ≤40% (HR: 2.26; 95% CI: 1.01 to 5.05) were associated with cardiac death on univariate Cox regression analysis. IS%LV ≥25% was not associated with cardiac death in a univariate Cox model (HR: 1.77; 95% CI: 0.80 to 3.89).

TABLE 2 Association of Patient Characteristics With MACE at 2 Years: Univariate Cox Regression Analysis

	HR	95% CI	p Value
Demographics			
Age	1.60	1.11–2.31	0.01
Sex	1.34	0.89–2.00	0.16
CV risk factors			
Diabetes	1.66	1.09–2.53	0.02
Hypertension	0.97	0.67–1.42	0.89
Anterior MI	1.30	0.90–1.87	0.16
Angiographic variables			
Multivessel disease	1.65	1.13–2.40	0.009
TIMI flow grade after PCI	3.31	1.70–6.43	<0.001
CE-CMR variables			
Presence of MO	4.68	2.86–7.66	<0.001
IS%LV ≥25%	2.04	1.42–2.92	<0.001
LVEF ≤40%	3.45	2.40–4.97	<0.001
LVESV index	1.03	1.02–1.04	<0.001
LVEDV index	1.02	1.01–1.02	<0.001

CI = confidence interval; HR = hazard ratio; MACE = major cardiovascular events; other abbreviations as in **Table 1**.

Independent predictors on multivariate Cox regression and their respective aHRs for cardiac death at 2 years are summarized in **Table 6**. MO was associated with the occurrence of cardiac death (aHR: 13.22; 95% CI: 1.75 to 99.82) when adjusted for age (aHR: 2.21; 95% CI: 0.96 to 5.06) and LVEF ≤40% (aHR: 1.66; 95% CI: 0.74 to 3.75).

DISCUSSION

The main findings of this study were that: 1) MO was present in >50% of patients with STEMI reperfused by pPCI (even in patients with TIMI flow grade post pPCI of 3, MO was present in >50% of patients); 2) MO, IS%LV, and LVEF were predictors for MACE, with value added to clinical risk factors; 3) MO was

TABLE 4 Incremental Value (c-Statistic) of MO, IS%LV, and LVEF ≤40% in the Prediction of MACE at 2 Years

	c-Statistic
Model a: age + multivessel disease + TIMI flow grade after PCI	0.59
Model b: age + multivessel disease + TIMI flow grade after PCI + IS%LV ≥25%	0.61
Model c: age + multivessel disease + TIMI flow grade after PCI + LVEF ≤40%	0.66
Model d: age + multivessel disease + TIMI flow grade after PCI + LVEF ≤40% + IS%LV <25%	0.66
Model e: age + multivessel disease + TIMI flow grade after PCI + LVEF ≤40% + MO	0.70

Abbreviations as in **Tables 1 and 2**.

TABLE 5 Association of Patient Characteristics With Cardiac Death at 2 Years: Univariate Cox Regression Analysis

	HR	95% CI	p Value
Demographics			
Age	2.18	0.95–5.01	0.07
Sex	1.33	0.50–3.54	0.57
CV risk factors			
Diabetes	2.25	0.96–5.25	0.06
Hypertension	1.05	0.44–2.49	0.91
Anterior MI	1.41	0.64–3.10	0.40
Angiographic variables			
Multivessel disease	0.78	0.35–1.76	0.55
TIMI flow grade after PCI	2.51	0.58–10.87	0.22
CE-CMR variables			
Presence of MO	15.02	2.01–112.24	0.01
IS%LV ≥25%	1.77	0.80–3.89	0.16
LVEF ≤40%	2.26	1.01–5.05	0.05
LVESV index	1.01	0.99–1.04	0.22
LVEDV index	1.00	0.98–1.02	0.91

Abbreviations as in **Tables 1 and 2**.

associated with cardiac death when adjusted for age and LVEF; and 4) IS%LV, adjusted for MO and LVEF, was not an independent predictor of MACE or cardiac death.

Previous studies that evaluated the prognostic value of MO, IS%LV, and LVEF in STEMI patients were limited by the inclusion of relatively small study sample sizes; evaluated composite clinical endpoints with "soft" components, including revascularization or angina; and were single-center studies (7–13). In the present internationally representative patient pooled analysis, we were able to assess the impact of CE-CMR variables on more clinically relevant events. With a sample size of 1,025 patients, the statistical power of the present pooled analysis was increased compared with that of previous single-center studies, which led to more robust predictions.

Our finding that the value of IS%LV, measured within 14 days after STEMI, is secondary to those of MO and LVEF is remarkable. It is important to realize

TABLE 6 Association of Age, MO, and LVEF ≤40% With Cardiac Death at 2 Years: Multivariate Cox Regression Analysis

	aHR	95% CI	p Value
Age	2.21	0.96–5.06	0.06
Presence of MO	13.22	1.75–99.82	0.01
LVEF ≤40%	1.66	0.74–3.75	0.22

N = 760 patients, 25 events.
Abbreviations as in **Tables 1, 2, and 3**.

that IS%LV is correlated with LVEF; however, LVEF is affected by additional factors, such as previous cardiovascular conditions, which might explain the importance of LVEF as a predictor of MACE in the present study. However, the univariate association of IS with MACE, its correlation with LVEF, and its contribution to the model as shown by an improvement in the *c*-index suggest that IS%LV is an attractive option as an endpoint in studies investigating new treatments. The measurement of LVEF is influenced by the presence of stunned myocardium, the relevance of which remains a topic of research, because most CMR studies are performed 4 to 7 days after STEMI, when stunning may be only partially resolved.

The finding that MO was, in addition to IS%LV and LVEF, an independent predictor of MACE is in concordance with findings from previous single-center studies. In the largest study to date, by de Waha et al. (12), IS adjusted for TIMI risk score, MO, and LVEF was not an independent predictor of adverse outcomes. We draw the same conclusion in the present study, in which IS%LV and LVEF were analyzed as continuous variables.

The cause of the detrimental effect of MO remains speculative. Baks et al. (5) demonstrated that the presence of MO in dysfunctional myocardial segments was associated with significantly greater thinning of the myocardium compared with that in segments without MO at follow-up. In contrast to segments without MO, segments with MO demonstrated no improvement in segmental wall thickening in a follow-up study at 5 months. Nijveldt et al. (6) found that a significant proportion of patients with MO developed a significant increase in LV end-diastolic volume, with no improvement in LVEF, whereas patients without MO showed a significant improvement in LVEF, at 4 months of follow-up. Both of those studies suggest an important relation between MO and LV remodeling that potentially might result in heart failure used as a MACE, as in the present study.

In addition to having predictive value for congestive heart failure, MO seems to be an important predictor of cardiac death. Reasons for cardiac death in patients with MO have been demonstrated by Ito et al. (22). Patients with no-reflow more often had malignant arrhythmias, cardiac tamponade, and early congestive heart failure compared with patients without no-reflow. An explanation of those findings might have been the reduced end-diastolic wall thickness in MO-positive segments, which might result in an increase in wall stress in the affected and adjacent segments (5).

The findings from the present study demonstrate, in a large cohort, the prognostic value of MO in patients who sustained a STEMI. MO was present in >50% of the study population, even, importantly, in a large subgroup of patients with angiographic TIMI flow grade after PCI of 3. These findings suggest that pPCI is not optimal yet and that there is a need for future novel treatment strategies. Of the current variables, MO is still the best predictor and probably indicates which patients should be investigated further. Screening for arrhythmias and progressive dilation, with follow-up echocardiography or CE-CMR, could potentially identify a high risk for cardiac death. The findings of this study are relevant in CMR trial design for the evaluation of the effects of, for example, thrombectomy devices, vasodilators, coronary post-conditioning, cell therapy, and glycoprotein IIb/IIIa inhibitors (23) in patients with STEMI. It is advisable to use, in addition to the measurement of LVEF and IS%LV, MO as surrogate endpoint in CMR trials in STEMI patients as MO and IS%LV might be variables that represent separate pathophysiological processes.

STUDY LIMITATIONS. The results of our study should be viewed in light of limitations inherent to the design of meta-analyses of individual patient data. These limitations include publication bias, data-availability bias, unmeasured heterogeneity in the patients included, and the use of event adjudication by different clinical events committees (24).

CE-CMR was performed at a wide range of days (up to 14) after STEMI, at different time points after contrast injection, and with different concentrations of gadolinium-based contrast agents (25). These variations may have influenced the detection of MO and may have influenced the measurement of IS (26). CE-CMR analysis was conducted in different ways, which also might have influenced the measurements of IS and MO.

In this analysis, we evaluated the prognostic value of MO only, without investigation of the extent of MO. A previous study (12) showed that the extent of MO provided incremental prognostic information. Unfortunately, this variable was available in only one study and therefore could not be included in the pooled analysis.

In cases of missing data, variables that may have influenced the primary endpoint (e.g., extent of MO, myocardial salvage [27], and the presence of a hypointense infarct core [28]) were not taken into account. Due to a low cardiac death rate, we were not able to add more variables in the multivariate Cox regression analysis.

CONCLUSIONS

MO is an independent predictor of the occurrence of MACE and cardiac death at 2 years in patients with STEMI. IS%LV is not independently associated with the occurrence of MACE, but might be used, in addition to MO and LVEF, as a surrogate endpoint in clinical trials investigating new treatment options.

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KEY WORDS **cardiac magnetic resonance, infarct size, microvascular obstruction, myocardial infarction, prognosis**

APPENDIX **For a supplemental table, please see the online version of this article.**

5.3 Myocardial 'No Reflow' prevention.

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Myocardial 'No-Reflow' Prevention

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Abstract: Despite achievement of optimal epicardial coronary flow in the majority of patients treated for ST-segment elevation myocardial infarction (STEMI) by primary percutaneous coronary intervention (PPCI), myocardial no-reflow is a common phenomenon occurring in 5 to 50% of patients. The no-reflow phenomenon is a predictor of infarct size and an independent predictor of mortality both in the short and long term. Prevention of no-reflow is therefore a crucial step in improving prognosis of patients with STEMI. Several strategies including pharmacological and mechanical ones have been developed to improve microvascular perfusion in the setting of a myocardial infarction. Prevention starts by conservation of the microvascular reserve especially in patients at high risk of acute coronary syndromes such as diabetes patients. Optimal glycaemic control and the use of statins have been shown to reduce no-reflow in this context. Reducing ischaemic time by shortening door to balloon times, administration of intracoronary GP IIb/IIIa antagonists during PPCI and the use of manual aspiration thrombectomy have been shown to result in better myocardial perfusion and improved clinical outcome in major trials. In this review we discuss some of these major trials and studies of other therapeutic options that aim to prevent the no-reflow phenomenon.

Keywords: Myocardial infarction, no-reflow phenomenon, microcirculation, infarct size, pharmacological prevention, mechanical prevention.

INTRODUCTION

No-reflow occurs in a significant number of patients presenting with acute myocardial infarction. The incidence ranges from 5-50% according to the sensitivity of the method used to assess no-reflow and to the study population. [1] The presence of no-reflow is a predictor of adverse events including a higher rate of post infarction complications, left ventricular remodelling, congestive heart failure and death in ST-segment elevation myocardial infarction (STEMI) patients [2, 3].

The phenomenon is also a dynamic process and the incidence depends in part on the timing of assessment. In fact resolution of the phenomenon as assessed by serial measurement using various modalities has been associated with favourable outcome as indexed by left ventricular remodeling [4].

Therefore prevention of this phenomenon is desirable and should lead to a reduced infarct size and improved survival both in the short and in the long term [5]. In this literature review we summarise the findings of important studies and trials that have evaluated the effect of pharmacological and mechanical therapeutic strategies that have been developed to prevent myocardial no-reflow in humans.

The various diagnostic indices available that have been utilised in trials studying this phenomenon are used interchangeably and accordingly throughout this review. These include ST-segment resolution, thrombolysis in myocardial infarction (TIMI) flow grade or frame count, [4, 6, 7] myocardial blush grade (MBG) [2], Index of microcirculatory resistance, [8] Intracoronary myocardial contrast echocardiography (MCE) [9, 10] microvascular obstruction by cardiac magnetic resonance imaging (CE-CMR)[11]. Details of the differential importance and diagnostic sensitivity and specificity of each has been described in the first part of this hot topic.

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PREVENTION OF MYOCARDIAL NO-REFLOW

Identification of therapeutic targets for prevention of no-reflow requires detailed understanding of its pathophysiological mechanisms. This is illustrated in Fig. (**1**). In principle strategies that target any of the known key steps in the cascade should minimise the risk of developing this phenomenon. Moreover, the effect is likely to be greater if the treatment is given earlier, that is closer to the initial events that trigger the cascade.

INDIVIDUAL SUSCEPTIBILITY TO MICROCIRCULATORY INJURY

The coronary microcirculation is subject to disease states, especially metabolic diseases that may be similar to microvascular involvement of the renal, retinal and neurological systems. Therefore the microcirculatory reserve or microcirculatory resistance index, largely depends on the extent of involvement by chronic disease such as diabetes mellitus, renal failure as well as on previous myocardial events from previous myocardial infarctions or even subclinical embolisations from plaque ruptures. Ischaemic preconditioning on the other hand is thought to be beneficial since it offers microvascular protection during an acute epicardial vessel occlusion by mechanisms that include collateral circulation [8].

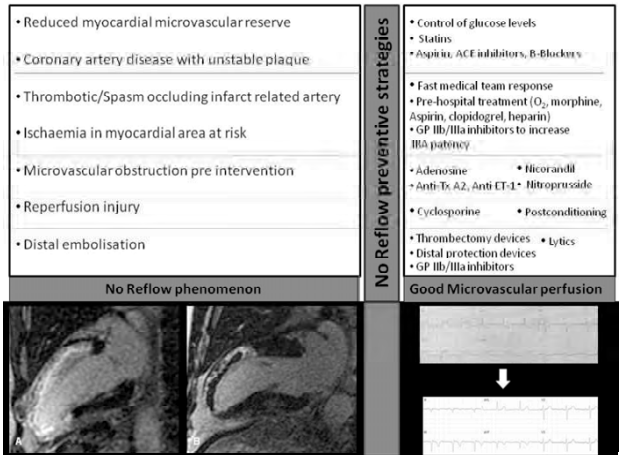

Fig. (1). Prevention of no-reflow phenomenon. Schematic illustration of preventive pharmacological and mechanical measures to prevent no-reflow according to the point of action in the pathophysiological cascade of ST elevation myocardial infarction. Any beneficial measure that intervenes in the cascade should be able to demonstrate a reduction in the no-reflow phenomenon by whichever means this is diagnosed. Microvascular obstruction on magnetic resonance imaging and ST segment resolution are two of the commonly used measures of microvascular perfusion.

The baseline status or the 'health' of the microcirculation most likely plays a crucial role in determining the extent of damage that it can sustain from an acute ischaemic insult. Both genetic and acquired susceptibility to microvascular injury may determine the occurrence and outcome of no-reflow as elegantly described by Niccoli *et al.* [12] Genetic predisposition is supported by evidence of association of polymorphism of the 2A receptor gene, possible lysis resistance and altered inflammatory cell response with no-reflow. On the other hand acquired predisposition occurs in disease states such as diabetes and hypercholesterolemia. Optimal control of such disease states may prove to be an excellent preventive strategy for development of no-reflow once an STEMI occurs as exemplified by the beneficial effect of statin treatment and insulin on no-reflow and infarct size respectively [13-15].

ISCHAEMIA-RELATED INJURY

Time to Reperfusion

In the first demonstration of the no-reflow phenomenon, Kloner *et al.* noted that the time of epicardial coronary artery occlusion (40 minutes versus 90 minutes in the animal model) was crucial in determining the microvascular damage that ensued [16]. Multiple clinical studies have also confirmed the importance of re-establishing flow as soon as possible after symptom onset. Utilising angiographic MBG as a measure of mircrovascular perfusion, Brodie *et al.* [17] showed that a shorter time to reperfusion was associated with smaller infarct size and trends for better myocardial blush which in turn reflected in lower 6-month mortality rates. Importantly, incremental delays in reperfusion after 2 hours had little impact on infarct size. Not surprisingly, no-reflow as measured with contrast enhanced magnetic resonance imaging (CE-MRI) also showed this time dependence with microvascular obstruction increasing from 0.5% to 1.5% to 3.7% and 6.6% as time to reperfusion increased from 90 minutes to 150 minutes to 150-360 minutes and >360 minutes [18]. Here again, salvaged myocardium is markedly reduced when reperfusion occurs after more than 90 min of coronary occlusion. Efforts to re-canalize occluded arteries have appropriately been focused on minimising delays between symptom onset and administration of effective treatment. Patient education to recognise symptoms and to seek immediate medical attention, prompt transport to a PPCI capable centre, minimisation of door to balloon times may all contribute to prevent the no-reflow phenomenon by decreasing ischaemic time.

Since most patients experience acute symptoms at home or even present to non- PPCI capable centres, administration of a pre-hospital treatment that restores patency of the infarct related artery (IRA) even before definitive treatment is desirable [19]. To this effect several randomised trials have been conducted to evaluate the benefits of pre-hospital thrombolysis. The largest trial to date, the ASSENT-4 trial (Assessment of the Safety and Efficacy of a New Thrombolytic) which studied a facilitated strategy with full dose tenecteplase, had to be prematurely terminated due to a higher mortality in this arm [20]. Notably a TIMI flow 0 was present in 24% in the facilitated group versus 62% in the conventional PCI arm and patients receiving the thrombolytic pre-hospital had the shortest delay to reperfusion and also the lowest 90 day mortality [21]. Although facilitation cannot be recommended based on this trial, this data from the post-hoc analysis adds evidence that early reperfusion with pharmacological means is beneficial especially if PPCI is expected to be delayed beyond 3 hours.

GPIIb/IIIa Inhibitors

The primary target of GP IIb/IIIa antagonists is platelet function and therefore the benefit of such agents in no-reflow prevention is achieved via prevention and/or resolution of microvascular thrombosis. However other mechanisms independent of platelet inhibition may play a role. These could include inhibition of adhesion of activated leucocytes to the microvascular endothelium through inhibition of $\alpha^5\beta^3$ MAC-1 and vitronectin receptors [22].

The three most studied GP IIb/IIIa inhibitors are abciximab, tirofiban and eptifibatide. Though similar to abciximab, tirofiban dissociates from the GP IIb/IIIa receptor more rapidly than abciximab. Its anti-aggregatory effects reverse within hours after the completion of the infusion, whereas abciximab binds near irreversibly to the receptor resulting in a considerably longer effect. Additionally, tirofiban does not inhibit other β3 integrins, such as the vitronectin receptor, at the surface of vascular cells or the activated MAC-1 receptor on leucocytes which have been traditionally regarded as crucial targets to explain abciximab effects on microcirculation.

The beneficial clinical effects of adjunctive GP IIb/IIIa inhibitors has been confirmed in a number of large randomised trials (RCT) [23, 24]. The ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up) trial showed that abciximab (ReoPro, Centocor, Malvern, Pa.) given to patients before PPCI as bolus of 0.25 mg per kilogram of body weight, followed by a 12-hour infusion of 0.125 g/Kg/min, improved both TIMI grade 3 flow as well as clinical outcome. Abciximab in combination with stent placement was shown to reduce both the incidence of acute ischemic events and the incidence of end points related to clinical restenosis. Benefits observed include a higher likelihood of successful reperfusion of the occluded IRA, improved success of stenting, reduction in the rate of reocclusion, and a more frequent restoration of an optimal flow for up to six months, with concomitant improvements in both left ventricular ejection fraction and prognosis [24].

Another RCT with 400 STEMI patients confirmed the improved myocardial perfusion achieved by GP IIb/IIIa antagonists. Antoniucci *et al.* [25] assessed prevention of no-reflow by early ST-segment resolution which was better achieved in the abciximab group (85% versus 68%, $p < 0.001$). Infarct size, as assessed by one-month technetium-99m sestamibi scintigraphy, also revealed smaller infarcts in the abciximab group. At six months both the cumulative difference in mortality between the groups increased (4.5% versus 8%), and the incidence of the composite of six-month death and re-infarction was lower in the abciximab group. Based on these positive results, abciximab is recommended as a preventive modality of no-reflow (Class IIa level of evidence B) [26].

INTRACORONARY VERSUS INTRAVENOUS GP IIB/IIIA INHIBITOR ADMINISTRATION

Intracoronary rather than intravenous administration of abciximab may improve microvascular perfusion. In an RCT comparing these two methods of administration, both the CMR determined microvascular obstruction (MVO) and the median infarct size (15.1% versus 23.4% p=0.01) were reduced with the intracoronary administration. Myocardial perfusion measured as early ST-segment resolution was also significantly improved in intracoronary patients with an absolute ST-segment resolution of 77.8% versus 70.0% p=0.006). This additional benefit could be due to higher concentration achieved with the intracoronary route which may facilitate the diffusion of the antibody to platelets inside the flow-limiting thrombus, thus resulting in improved dissolution of thrombi and microemboli at the ruptured plaque and further downstream in the microcirculation [27]. The recent CICERO Trial (Comparison of Intracoronary Versus Intravenous Abciximab Administration During Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction) looked into this difference in mode of administration in patients undergoing also thrombus aspiration [28]. This time no difference in the primary endpoint ST-segment resolution was found between intracoronary and intravenous administration. On the contrary, MBG at 30 days and enzymatic infarct size were significantly reduced in the intracoronary abciximab-treated group, suggesting a clinical benefit that becomes evident later. This effect on clinical endpoints is currently being studied in an ongoing trial [29]. Local administration of GPIIb/IIIa inhibitors as well as other pharmacological agents aimed at improving myocardial perfusion can also be administered via infusion catheters such as the ClearWayRX Therapeutic Perfusion Catheter (Atrium Medical Corporation, Hudson, NH, USA). Current studies such as the COCTAIL (ClearWayRX system to reduce intracoronary thrombus in patients with acute coronary syndromes according to optical coherence tomography after abciximab intracoronary local infusion) trial and the INFUSE-AMI (intracoronary abciximab infusion and aspiration thrombectomy in patients undergoing percutaneous coronary intervention for anterior ST-segment elevation myocardial infarction) study will provide us with more data on the efficacy of this mode of intracoronary administration [30, 31]. The COCTAIL will compare the use of the infusion catheter to conventional infusion via the guiding catheter. OCT derived thrombotic burden is the primary endpoint for the COCTIAL trial while MBG and corrected TIMI frame counts will be used as markers to compare microcirculatory function between the two modes of administration. The INFUSE-AMI on the other hand is testing the hypothesis that the intracoronary administration of an abciximab bolus through the ClearWay catheter with or without thrombus aspiration before stent implantation compared to no infusion with or without thrombus aspiration reduces infarct size among patients undergoing PPCI for anterior STEMI who are treated with bivalirudin. In this study MRI derived infarct size will be the primary end point while MRI derived microvascular obstruction is amoung the secondary endpoints.

PRE-HOSPITAL VERSUS PERIPROCEDURAL GP IIB/IIIA INHIBITOR ADMINISTRATION

Early rather than periprocedural administration of GP IIb/IIIa antagonist inhibition is intuitively beneficial as restoration of epicardial flow is more commonly achieved when this drug is administered pre-hospital. This advantage of a shorter ischaemic time and better TIMI flow and myocardial

flow pre-procedurally does not seem to influence positively the incidence of myocardial no-reflow post-procedurally as illustrated by various RCT's [32-34].

The On-TIME trial (Ongoing Tirofiban In Myocardial Infarction Evaluation) is one of the largest trial investigating the benefits of early versus late GP IIb/IIIa inhibitors. Five hundred and seven patients who were transferred to a PCI capable centre were randomised to pre-hospital initiation of tirofiban or initiation in the cardiac catheterisation laboratory. A higher rate of pre-procedural TIMI 2-3 flow was achieved in the early group as was preprocedural myocardial perfusion (MBG 2 30% versus 22%, p=0.04) and a lower thrombus burden. These parameters were not any different between the two arms postprocedurally and additionally there was no effect on the one-year rate of death (4.5% versus 3.7%, p=0.66) or re-infarction (2.4% versus 3.7%, p=0.43) [35]. The TITAN-TIMI 34 also showed similar results with eptifibatide with better pre-PCI TIMI myocardial perfusion in the group receiving the drug earlier (24% versus 14%, p = 0.026) [36].

Several other trials looked into this strategy of facilitation by GP IIb/IIIa inhibitors and two metaanalysis by Montalescot *et al.* [37] and De Luca *et al.* [38] summed up some of these major trials. In the first, 6 trials enrolling 931 STEMI patients treated with abciximab (3 trials) or tirofiban (3 trials) in combination with PPCI were analysed. Coronary patency was improved with early administration as depicted by a higher rate of TIMI grade 2 or 3 flow (41.7% versus. 29.8%), (OR, 1.69; 95% CI, 1.28-2.22; p<.001). The authors also report a non-significant 28% reduction in mortality from 4.7% to 3.4% with early administration of GP IIb/IIIa inhibitors and similar trends for reinfarction and a composite ischemic end point. In the second metaanalysis – EGYPT (Early glycoprotein IIb-IIIa inhibitors in primary angioplasty) - including individual patient level data (1662 patients) from 11 trials, reported similar benefits for early drug administration. Thus preprocedural TIMI 3 flow (23.0% versus 13.3%, p <0.0001) and complete ST-segment resolution (60.3% versus 54.1%, p=0.02) were significantly improved. Although favourable trends were observed in terms of post procedural TIMI 3 (90% versus 87.9% p= 0.18) and MBG 3 (49% versus 45.8%, p=0.018), no difference in mortality was observed (3.7% versus 4.7%, HR [95% CI] 0.78 [0.49-1.26], p=0.3). In a pre-specified analysis testing the heterogeneity in treatment effect with different GP IIb/IIIa inhibitors, early abciximab administration did improve survival (2.6% versus 6.5%; HR [95% CI] 0.39 [0.17-0.9], p=0.026). This favourable clinical outcome was substantiated by demonstration of better indices of lower incidence of myocardial no-reflow in patients given this particular antiplatelet early versus periprocedurally. The lack of clear data from trials to prove a translation of the improvement observed with up-front platelet inhibition may be explained by confinement of this potential benefit to high risk subgroups. In fact registry data analysis by Rakowsky *et al.* suggest mortality benefit in patients with TIMI risk score of 3 [39].

PRE-INTERVENTION LYTICS AND GPIIB/IIIA INHIBITORS

The FINESSE trial (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) randomised 2500 STEMI patients within 6 hours of symptom onset to PPCI facilitated with pre-catheterization laboratory administration of abciximab with half-dose reteplase (combination-facilitated group), abciximab alone (abciximab-facilitated group), or with abciximab administered immediately before the procedure [40]. Early abciximab did not confer superiority over periprocedural abciximab whereas combination facilitation improved preprocedural reperfusion. This effect was also reflected in an angiographic substudy (n=637) of this trial by Prati *et al.* that looked into the effect of these treatment strategies on no-reflow [41]. In fact, although patients in the combination-facilitated group had significantly higher rates of baseline IRA patency compared with the abciximab-facilitated and the PPCI groups (76.1% versus. 43.7% and 32.7%), no significant differences were noted in the post-PCI corrected TIMI frame count or the rates of post-PCI TIMI flow grade 3 (79.8%, 77.7%, and 76.6%) or MBG 2/3 (85.6%, 79.5%, and 86.4%). Again this study suggests that benefits of early pharmacological IRA recanalisation in a setting of timely PPCI is not universally beneficial.

INTRACORONARY STREPTOKINASE

The intracoronary administration of lytic agents is an attractive option that may be more potent than any other pharmacological agent in dissolving intracoronary thrombi. The effect of streptokinase on microvascular perfusion was investigated in a small prospectively randomised pilot trial [42]. Using the highly sensitive index of microcirculatory resistance measures two days after the PPCI, the authors reported a better microvascular perfusion (16.29+/-5.06 U versus 32.49+/-11.04 U), in patients treated with intracoronary streptokinase. The additional use of low dose (250 kU) and intracoronary administration of streptokinase (on top of an antithrombotic/antiplatelet regimen that already includes GP/IIb/IIIa inhibitors, heparin, aspirin and clopidogrel) would, in principle achieve its desired effects without increasing the risk of bleeding. However the risk/benefit of this strategy would need to be confirmed in a larger RCT.

Adenosine

Adenosine, an endogenous purine nucleoside is a potent vasodilator of the microcirculation and has been an attractive therapeutic tool in the management of no-reflow. Mechanisms other than vasodilation such as inhibition of polymorphonuclear leucocytes which therefore prevents adhesion onto the endothelial cell surface have been implicated. The role of this drug administered upfront in preventing the no-reflow phenomenon has been investigated in a number of randomised studies.

In the thrombolyis era, a large trial set to affirm the role of adenosine, had to be terminated early due to lack of effect on the primary endpoints which included global and regional left ventricular systolic and diastolic function, as assessed by two-dimensional and Doppler echocardiography before hospital discharge [43]. Results with the application of this pharmacological agent were however encouraging in patients undergoing PPCI. In fact a small randomised study with 54 patients, a distal intracoronary adenosine bolus was associated with a lower incidence of the no-reflow phenomenon with only one patient in the treatment group as compared to

7 in the placebo group [44]. These positive initial data were not reproduced in a larger trial recently published trial by Desmet *et al.* [45]. In this study 112 STEMI patients were randomised to selective intracoronary injection of 4mg of adenosine versus conventional treatment. CE-MRI determined myocardial salvage and microvascular obstruction was not improved in the adenosine group. Myocardial blush grade, and ST-segment resolution were also similar and the treatment had no effect on infarct size at 4 months. Further, the intracoronary injection of high dose adenosine (2 x 120μg rather than 30-60μg) does not seem to prevent no-reflow in PPCI patients undergoing routine thrombus aspiration [46].

The role of adenosine may in fact be more important for the treatment rather than prevention of no-reflow. A higher intravenous dose of adenosine (70 μg/kg/min) that was started at the time of thrombolysis or before coronary intervention and continued for 3 hours in STEMI patients did however have a positive effect on infarct size in the AMISTAD II trial (Acute Myocardial Infarction STudy of Adenosine) [47]. The study was however underpowered to confirm the reduction in clinical events in the higher dose subgroup. Thus further studies may be warranted to affirm this effect with higher prolonged doses in an era of PPCI.

Nitroprusside

Sodium nitroprusside is a direct nitric oxide donor and very effective microvascular vasodilator. Initial observational studies of the use of this agent for treatment of no-reflow were encouraging [48]. However the selective injection of the drug (60μg diluted in 5 mls as intracoronary bolus) in the IRA as primary prevention of no-reflow remains debatable since an RCT showed no improvement in ST-segment resolution, myocardial blush score despite improvement in clinical outcomes at 6 months [49]. On the other hand in an observational study with 120 patients, Shinozaki *et al.* reported a 60% reduction in the incidence of no-reflow as well as improvement in other parameters of epicardial coronary flow [50]. A dose of 120μg was used in this study suggesting a better effect of nitroprusside at such a higher dose, however these findings this will need to be confirmed in an adequately powered RCT.

Nicorandil

Nicorandil is a hybrid drug with ATP-sensitive potassium channel opener and nicotinamide nitrate. It decreases infarct size possibly by suppressing free radical generation and by modulating neutrophil activation [51]. In an RCT by Ito *et al.* the frequency of sizable MCE defined no-reflow phenomenon was significantly lower in a group treated by nicorandil than in the control group (15% versus 33%, $p < 0.05$) [52]. In a larger RCT with 368 patients, intravenous nicorandil (12 mg given over 20-30 minutes prior to PPCI) showed better ST-segment resolution (79.5% and 61.2%) as well as fewer events at 2.4 years of follow-up [53].

Reperfusion Injury

Hypothermia

Animal studies have long established that cooling exerts a protective effect on myocytes during ischemia which reflects into a reduced infarct size [54]. The same effect has been demonstrated for the no-reflow phenomenon in the rabbit model. In fact hypothermic therapy initiated late during ischemia and continuing for several hours of reperfusion significantly improves reflow and reduces macroscopic zones of no-reflow and necrosis in this model [55]. Initial clinical experience with this is limited but promising. Götberg *et al.* have shown in a small randomised study with 20 patients that by reducing core temperature to <35°C using controlled infusion of 4°C cold saline using pressure bags, infarct size is reduced as measured by CMR [56]. Further studies are needed to confirm these findings but if reproducible it is likely that hypothermia will have the same positive effect on the no-reflow phenomenon as it showed on infarct size.

Cyclosporin

Cyclosporine inhibits the opening of mitochondrial permeability-transition pores and has been shown in animal models to attenuate lethal myocardial injury that occurs at the time of reperfusion. In a pilot clinical randomised study that enrolled 58 patients, an intravenous bolus of cyclosporine (2.5 mg/Kg) before undergoing PCI, creatine kinase was reduced as was the MRI-determined infarct size (37 g versus 46 g, p=0.04) [57]. These encouraging results do warrant larger trials to further evaluate this effect.

Postconditioning

Repeated episodes of ischaemia by balloon occlusion results in attenuation of irreversible myocardial injury in the dog heart [58]. The clinical application of this effect has been demonstrated in a small randomised study with 30 patients [59]. The postconditioning group had 4 episodes of 1-minute inflation and 1-minute deflation of the angioplasty balloon performed within 1 minute of reflow. Area under the curve of creatine kinase release was significantly reduced in the postconditioning compared with the control group (208 versus 326) i.e. a 36% reduction in infarct size. Myocardial blush grade was also significantly increased in postconditioned compared with control subjects. Similar effects on infarct size in animal studies has been obtained with remote postconditioning such as obtained by inducing ishaemia in a limb by repeated blood pressure cuff inflations [60]. Initial experience in humans seems promising but further studies are required to understand the potential reduction in no-reflow and possibly, more realistically, which specific patient groups might benefit from this treatment [61].

Endothelin-1 Antagonists

Endothelin-1 antagonsits have been identified as a potential agent to prevent no-reflow. It targets endothelin-1 which has vasoconstrictive effect on coronary arteries, enhances neutrophil adhesion to the endothelium and induces elastase release which is implicated in tissue injury [7, 62]. The ET-1 antagonist has been shown to show beneficial effects on reperfusion in animal models as demonstrated by MCE. The clinical application of such an agent is still unexplored.

Other Potential Therapeutic Targets

Neutrophil counts, mean platelet volume, platelet reactivity and thromboxane A2 have all been shown to be closely

associated or even predict no-reflow [63-66]. Pharmacological modulators of these factors may in the future be key potential targets in no-reflow prevention.

PREVENTION OF ATHEROTHROMBOTIC EMBOLISATION

Plaque rupture produces intraluminal debris that is often thrombogenic Fig. (**2**). The distal embolisation of this material adversely affects coronary capillary flow especially particulate matter >200-μm in diameter [67]. Measures that prevent this complication which is often perpetuated or even triggered by insertion of intracoronary instruments with large profiles and by stent deployment during PPCI, are therefore likely to improve microcirculatory flow [68].

THROMBUS LOAD AND THE NO-REFLOW PHENOMENON

Patients who present with angiographic high thrombus load (especially if graded after introduction of the guide wire beyond the occlusion in the IRA) have a higher risk of no-reflow and epicardial artery distal embolisation which clearly transmits into a higher cardiac mortality rate at 30 days [69]. The thrombus load and occurrence of no-reflow in an era of drug eluting stent implantation for acute myocardial infarction is of major interest since safety concerns are still unresolved following registry reports of a higher rate of stent thrombosis in these high risk acute myocardial infarction patients [70]. Therapeutic strategies aimed at reducing thrombus load by mechanical thrombus removal, thrombolysis or pharmacological thrombolysis have been studied to date. Other treatment strategies targeted distal embolisation. These studies are listed in (Table **1**) and summarised below.

MECHANICAL THROMBUS REMOVAL

Effective mechanical clearance of thrombotic material is desirable. Apart from a reduction in potentially embolic material, reduction in thrombus load, often leads to a clearer angiographic definition of the stenotic culprit lesion which may avoid unnecessary balloon predilatations and thereby allows more frequent application of direct stenting (DS). Thrombus aspiration can be accomplished by manual aspiration that connects the aspiration catheter to a syringe with vacuum. Alternatively a vacuum pump can be connected to effect aspiration.

The efficacy of the Rescue catheter (Boston Scientific/Scimed, Inc, Maple Grove, Minn) was tested in a Danish RCT [71]. This thrombectomy system is made up of a 4.5F polyethylene catheter that is advanced over a guidewire through a 7F guiding catheter. The proximal end of the catheter has an extension tube connected to a vacuum pump (0.8 bar) with a collection bottle. The study which randomised 215 patients to thrombectomy versus conventional PCI failed to show an advantage of this technique and to the contrary in the thrombectomy group, final infarct size assessed by sestamibi SPECT was larger (median, 15%; [interquartile range, 4% to 25%] versus 8% [interquartile range, 2% to 18%]; P=0.004). Importantly no-reflow as assessed by ST-resolution was not different between the groups.

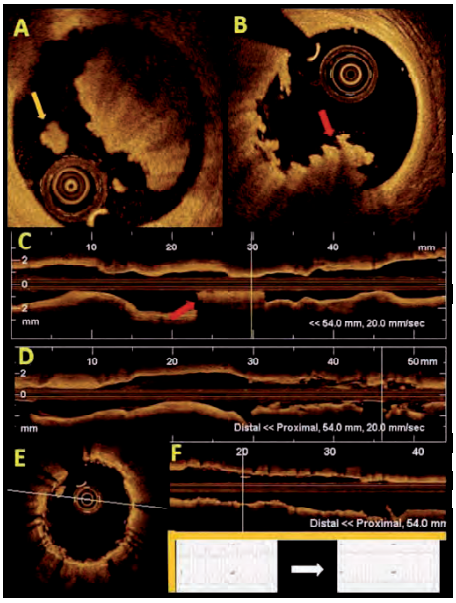

Fig. (2). The importance of thrombectomy during primary PCI to prevent the no-reflow phenomenon. Optical Coherence Tomography images from the right coronary artery of a patient presenting with acute ST segment elevation myocardial infarction. Intraluminal atherothrombotic material (arrows) can be observed in the cross-sectional images (**A**, **B**). Thrombus that is free floating (yellow arrow) may be more likely to embolise than mural thrombus (red arrow) or larger thrombi (small arrows). A longitudinal view in panel **C** also shows the thrombotic mass. Thrombus removal has significantly reduced the atherothrombotic material mass as seen in **D**. After thrombectomy and stent implantation in the same segment, intraluminal thrombotic material is reduced to a minimum (**E**, **F**). The patient had >70% reduction in ST segment elevation 1 hour after the procedure (lower right panel) indicating a satisfactory microvascular perfusion.

In another multicenter trial - VAMPIRE (VAcuuM asPIration thrombus Removal)- 355 presenting even up to 24 hours from onset of STEMI symptoms were randomised to treatment with a Nipro's TransVascular Aspiration Catheter (Osaka, Japan) versus conventional PCI. This time a trend toward lower incidence of slow or no-reflow in patients treated with aspiration versus conventional PPCI (12.4% versus 19.4%, $p = 0.07$) was observed. Moreover the rate of achievement of MBG 3 was higher in the aspiration group (46.0% versus 20.5%, $p < 0.001$). The inclusion of patients up to 24 hours allowed identification of a more pronounced effectiveness of aspiration in patients presenting after 6 h of symptoms onset.

Table 1. Major Randomised Trials of Pharmacological Agents Studied for the Prevention The No-Reflow Phenomenon

Trial	Adjunctive device	Number STEMI patients	Additional GP IIb/IIIa antagonists	Stents implanted	Primary end-point/s	Measure of no-reflow	Distal Emboli	MBG	ST resolution	Infarct Size	30 day mortality	Follow-up (months)	Long term mortality
EMERALD [83]	Distal protection: GuideWire Plus	501*	Not per protocol 83.3% vs. 83.5%	96.8 vs. 96.8	>70% ST resolution 30 min after last injection Infarct size Tc 99m sestamibi	ST resolution	9.3% vs 5.8% P=0.17	85 vs 78.9 P=NS	63.3 vs 61.9 p=NS	Sestamibi 12.0 vs. 9.5 p =0.15	2.0% vs. 2.9% p=0.53	6	3.4% vs 3.3% p=0.94
DEDICATION [84]	Distal protection Filter-Wire-EZ or Spider X	626	Per protocol 97% vs. 96% p=0.36	98 vs. 99 p= 0.29	70% ST resolution at 90 min after PCI	ST resolution			76 vs. 72 p=0.29	CK-MB 185 vs. 184 p=0.99	2.6% vs. 2.5% p=1	15	4.2% vs. 4.8% p=NS
X-AMINE ST [82]	X-Sizer	201	Not per protocol 55% vs. 65% P=NS	100 vs. 99 p=NS	Degree of ST resolution 60 minutes after procedure	ST resolution >50% resolution	2.1 vs. 10 p=0.033	75.3 vs 75 p= NS	7.5 vs 4.9 p=0.031 67.8 vs. 52.6 p=0.037	N/A	4% vs. 4% p=NS	6	6%vs. 4% p=NS
Kaltoft [71]	Rescue	215	Per protocol 96 vs. 93 p=0.37	95 vs. 97 p=1	Myocardialsalvage detected by ^{99m}Tc-sestamibi	ST resolution 90 min	9 vs. 6 p=0.49	N/A	62 vs. 60 p=0.94	15 vs. 7.5 p=0.004	0 vs. 1 p=NS	N/A	N/A
JETSTENT [81¶]	Rheolysis AngioJet	501	Per protocol 97 vs. 98 p=0.84	N/A	ST segment resolution at 30min. and Infarct size Tc 99m sestamibi	ST segment resolution at 30min TIMI blush grade 2	N/A	92.1 vs. 94.7 p=NS	85.8 vs. 78.8 p=0.043	Sestamibi 11.8 vs. 12.75 p=0.398	1.6 vs. 2.9 p=NS	12	3.2 vs. 6.4 p=NS
REMEDIA [72-73]	Diver (TA)	100*	For PPCI yes For rescue not 68% vs. 63.3% p=0.53	N/A	MBG 2 >70% ST resolution	MBG 2 >70% ST resolution + MCE substudy in 50 patients	8 vs. 17.8 p=0.19	68 vs. 44.9 p=0.02	58 vs. 36.7 p=0.034 CSI_t<CSI_{CPCI}	CK-MB 256 vs. 283 p=0.47	6% vs. 6.2% p=NS	N/A	N/A
DEAR MI [74]	Pronto (TA)	148	Per protocol 100%	99 vs. 97 p=NS	MBG 3 >70% ST segment resolution after procedure	MBG 3 >70% ST segment resolution after procedure	5 vs. 19 p=0.019	100 vs.94 P<0.0001	68 vs. 50 p=0.041	790 vs.910 p<0.0001	0 vs 0 p=1	N/A	N/A
EXPIRA [79¶]	Export (TA)	175	Per protocol Both 100%[#]	Both 100%	MBG 2 >70% ST resolution at 90min MVO & IS	MBG 2 >70% ST resolution MVO & IS	N/A	88.6 vs 59.8 p<0.001	63 vs. 39 p=0.001	CE-MRI 13 vs. 14 p=0.6	0 vs. 1 p=NS	24	0% vs. 6.8 p=0.0001

(Table 1) contd….

Trial	Adjunctive device	Number STEMI patients	Additional GP IIb/IIIa antagonists	Stents implanted	Primary end-point/s	Measure of no-reflow	Distal Emboli	MBG	ST resolution	Infarct Size	30 day mortality	Follow-up (months)	Long term mortality
TAPAS [75-76]	Export (TA)	1071	Per protocol 93.4 vs. 89.9 p=0.12	92.3 vs. 92 p=0.88	MBG 0 or 1	MBG 0or1 ST resolution	5.6 vs.5.8 p= 0.92	17.1 vs. 26.3 p=<0.001	56.6 vs. 44.2 p<0.001	CK-MB 58 vs. 63 p=0.46	2.1 vs. 4 p=0.07	12 months	3.6 vs. 6.7 p=0.02

The first percentage mentioned refers to the adjunctive thrombectomy group followed by the conventional PCI group. TA=manual thrombus aspiration

*Included patients with rescue percutaneous intervention after failed thrombolysis.[#] Patients with contraindication to GP IIb/IIIa antagonsists excluded from study. [¶] Only patients with thrombus grade 3-5 included. MCE= myocardial contrast echocardiography; CSI_T and CSI_{CPCI} contrast score index (exact values not published) MBG= myocardial blush grade; MVO= microvascular obstruction. IS = infarct size; both of the latter as determined by contrast-enhanced MRI.

Aspiration of thrombus can also be done in a simpler way as exemplified by the Diver CE (Invatec, Brescia, Italy) rapid-exchange, 6-F compatible, thrombus-aspirating catheter. This catheter has a central aspiration lumen and a soft, flexible, 0.026-inch, non-traumatic tip with multiple holes (one large anterior and three smaller lateral ones) communicating with the central lumen. A 30-ml luer-lock syringe is connected to the proximal hub of the central lumen for thrombus-aspiration. The REMEDIA (Randomized Evaluation of the Effect of Mechanical Reduction of Distal Embolisation by Thrombus- Aspiration in Primary and Rescue Angioplasty) was the first trial that assessed the role of thrombectomy with this simple manual aspiration catheter [72]. This strategy proved to be successful as myocardial perfusion indices including MCE in a substudy were significantly better that with conventional PPCI [73]. Although the study was underpowered for subgroup analysis, the effect of simple TA seemed to be more beneficial in patients presenting with an occluded IRA and those with a high thrombus load.

These results were echoed in a study published in the same period using a similar manual aspiration catheter, namely the Pronto extraction catheter (Vasc.solutions, Minneapolis, Minnesota). The DEAR MI (Dethrombosis to Enhance Acute Reperfusion in Myocardial Infarction) randomised 148 patients to standard PCI with stenting and abcximab or thrombus aspiration plus standard PCI. Complete ST-segment resolution occurred in 50% versus 68% ($p < 0.05$) and MBG-3 was achieved in 44% versus 88% ($p < 0.0001$) for the adjunctive treatment compared to conventional PCI respectively [74].

In the TAPAS trial (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) [75] 1071 STEMI patients were randomly assigned to thrombus-aspiration with a 6-French Export Aspiration Catheter (Medtronic) or conventional-PCI before undergoing coronary angiography. GP IIb/ IIIa inhibitors were used in all patients except for those with contraindications. Myocardial blush grade of 0 or 1, which was the primary end-point, occurred in a lower proportion of patients in the thrombus-aspiration group (17.1%) than in the conventional-PCI group (26.3%). Complete ST-segment elevation resolution occurred in 56.6% of the TA and 44.2% of the conventional PCI-group respectively. Interestingly in this trial, histopathologically confimed atherothrombotic material was aspirated in 72.9% of patients undergoing TA even though thrombus was initially visible in only nearly half of these patients. In fact subgroup analysis showed that TA benefitted all patient groups including those without visible thrombus. Intuitively patients revascularised within the first three hours from symptom onset have a higher degree of benefit from this adjunctive strategy. The reduced incidence of no-reflow transmitted into a significantly lower cardiac death at 1 year in the thrombus aspiration group (3.6%) versus (6.7%) in the conventional PCI group (hazard ratio [HR] 1.93; 95% CI 1.11-3.37; p=0.020). Added benefits in terms of repeat myocardial infarction were also suggested with a composite 1-year cardiac death or non-fatal re-infarction occurring in 5.6% of patients in the thrombus aspiration group and 9.9% of patients in the conventional PCI group (HR 1.81; 95% CI 1.16-2.84; p=0.009) [76]. To date the single centre TAPAS trial is the largest body of evidence that confirmed the benefits and utility of thrombus aspiration for patients with STEMI irrespective of clinical and angiographic characteristics at baseline. The study provided the necessary evidence needed for endorsement of this technique as a class IIa, level of evidence B indication in the ACC/AHA (American College of Cardiology/American Heart Association) as well as in the ESC (European Society of Cardiology) guidelines [26, 77].

The effect of manual thrombus aspiration on the no-reflow phenomenon as measured with contrast-enhanced MRI has also been demonstrated in the EXPIRA (Thrombectomy With Export Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention) trial [78]. Of the 175 patients enrolled, 75 patients with an anterior myocardial infarction were randomised 1:1 and formed a CE-MRI substudy. In the whole group, MBG 2 and ST-segment resolution occurred more frequently in the thrombus aspiration group (88% versus 60%, p = 0.001; and 64% versus 39%, p = 0.001). For the MRI substudy, microvascular obstruction, defined as the regions of hypointensity on the first-pass T1-weighted perfusion images, was significantly lower in the thrombectomy group (3.7 ±2.6 versus 1.7±1.9, p=0.0003.) Also at 3 months, infarct size was significantly reduced only in the thrombectomy group.

To date, various commercially available manual aspiration catheters have been developed with some differences in design. Specifically catheters with larger internal lumina have been developed with the purpose of increasing efficacy of aspiration of larger clots. However evidence shows that there is no difference in the size of particle retrieved and in microvascular perfusion between large-internal-lumen catheters (Diver, Invatec, Roncadelle, Italy) and medium-sized catheters (Export, Medtronic, Minneapolis, Minnesota) [79].

RHEOLYTIC THROMBECTOMY

Thrombectomy with the AngioJet rheolytic thrombectomy system (Medrad Interventional/Possis, Minneapolis, Minnesota) is accomplished with high-velocity saline jets contained within the distal catheter tip. These jets create a strong negative pressure (Bernoulli effect) that entrains the thrombus to the catheter inflow windows, where it is captured, fragmented, and evacuated from the body through the catheter and associated tubing.

The AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for acute Myocardial infarction (AIMI) [80] randomised 480 patients to rheolytic thrombectomy with Angiojet (Possis Medical, Minneapolis, MN, USA) versus conventional primary angioplasty. Infarct size as determined by technetium-99m sestamibi was higher in the rheolytic thrombectomy group (9.8 +/- 10.9% versus 12.5 +/- 12.13%; p = 0.03). The 30-day mortality was also higher in the rheolytic thrombectomy (RT) group. (0.8% versus 4.6%, p = 0.02). The negative results of this trial require careful interpretation since a low-risk population was studied, TIMI 3 flow at presentation was higher in the control group (27% versus 19%) and only 10% of patients had visible angiographic thrombus. In fact in a recent second trial, the JETSTENT (AngioJet Rheolytic Thrombectomy Before Direct Infarct Artery Stenting in Patients Undergoing Primary PCI for Acute Myocardial Infarction) 501 patients were randomised once there was angiographic evidence of thrombus grade 3 to 5, and a reference vessel diameter >/=2.5 mm [81]. This time ST-segment resolution was more frequent in the RT arm as compared with the DS alone arm: 85.8% and 78.8%, respectively (p = 0.043). However TIMI flow grade 3, corrected TIMI frame count, and TIMI grade 3 blush and infarct size were not different between the two treatment arms. Major adverse cardiac events (MACE) at 1, 6 and 12 months were lower in the RT arm driven primarily by a lower number of deaths and target vessel revascularisation. The improvement in trial design as well as attention to application of appropriate technique during RT (catheter activation at least 1 cm proximal to the thrombus, to create a suction vortex before advancing the device; advancing the thrombectomy catheter slowly (1 to 3 mm/s) to and through the thrombosed segment; restarting the thrombectomy at the end of the proximal-to-distal pass, with a distal-to-proximal pullback; second or third pass made if there was evidence of residual thrombus or a TIMI flow grade <2) may have contributed to the results from this study which re-opens discussion of the use of RT especially in patients with high thrombus load.

Another mechanical thrombolytic system that has been studied is the X-Sizer catheter system (X-Sizer catheter system; eV3, White Bear Lake, Minnesota). This device is a two-lumen over-the-wire system with a helical shape cutter at its distal tip. The cutter rotates at 2,100 rpm driven by a hand-held battery motor unit. One catheter lumen is connected to a 250-ml vacuum bottle, and aspirated debris is collected in an in-line filter. The X-AMINE ST trial randomised 201 patients to treatment with this device versus conventional PPCI and showed an improved post procedural ST-segment resolution [82]. Also angiographic distal embolisation was significantly lower when the thrombectomy system was employed. However MBG and clinical outcome was not different between groups.

DISTAL PROTECTION DEVICE

An early concept of distal protection is exemplified by the GuardWire Plus (Medtronic Corp, Santa Rosa, Calif) system which consists of a 0.014-in guidewire incorporating a central inflation lumen distally attached to an elastomeric balloon (0.028-in crossing profile, 2.5- to 5.0-mm diameter range). When the balloon is inflated, antegrade blood flow stops to allow intervention over the wire and subsequent aspiration of liberated debris suspended within a stagnant blood column via a 5F monorail Export catheter. By positioning the elastomeric balloon as close to the lesion as possible, exposure of unprotected side branches to embolic debris can be minimized. The EMERALD [83] (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris) multicenter trial enrolled 501 ST-segment elevation myocardial infarction (STEMI) patients presenting within 6 hours of symptom onset and undergoing PPCI or rescue intervention after failed thrombolysis and compared the strategy of distal protection with conventional angioplasty. In the distal protection group, aspiration prior to PCI was encouraged to diminish thrombus burden and improve distal visualization. All predilation and postdilation angioplasty balloon inflations, as well as stent implantation, were protected whenever possible. Visible debris was retrieved from 73% in the distal protection group. Complete ST-segment resolution was achieved in a similar proportion-63.3% with distal protection versus 61.9% without distal protection (absolute difference, 1.4% [95% confidence interval, -7.7% to 10.5%; p = 0.78]). Similarly, left ventricular infarct size determined by technetium Tc 99m sestamibi imaging was not different between groups (median, 12.0% versus 9.5%, p = 0.15) as was MACE at 6 months. (10.0% versus 11.0%, p = 0.66). Therefore despite effective retrieval of embolic debris, distal embolic protection with this system did not decrease no-reflow or have any positive impact on infarct size and subsequent adverse events.

Two other distal protection devices were studied in the DEDICATION (Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction) trial [84]. In this 2 center trial, either of two systems was employed, namely a filterwire (FilterWire-EZ, Boston Scientific, Santa Clara, California) or a SpiderX protection device (eV3, Minneapolis, Minnesota). As with the Guidewire Plus system, an important limitation with these distal protection devices is the lack of protection when crossing the lesion which may itself cause distal embolisation. Also the devices require a 'landing zone' which is not feasible in all cases. In fact the 626 STEMI pa-

tients enrolled in the trial, were randomly assigned to distal protection versus conventional PCI only once the distal bed was angiographically visible to ensure applicability of the device. Again no significant difference was found in the occurrence of the primary end point, that is, 70% ST-segment resolution 90 min after PCI (76% versus 72%, p = 0.29) Enzymatic infarct size was also not different: troponin-T (4.8 microg/l and 5.0 microg/l, p = 0.87) or maximum creatine kinase-MB (185 microg/l and 184 microg/l, p = 0.99). At 15 months, mortality was similar in the two groups whereas the higher MACE rate in the distal protection group (19.2% versus 13.7%) was driven primarily by increase target vessel revascularisation, notably with an increased stent thrombosis rate [85].

METAANALYSIS

The no-reflow phenomenon had been shown to be a good predictor or surrogate of cardiac mortality even up to five years [5] and therefore any study that demonstrates a reduction in no-reflow should result in a survival advantage [86]. However none of the individual studies of adjunctive thrombectomy published to date was adequately powered to assess its impact on long-term clinical outcome. Given that the long-term mortality rate for patients with optimal microvascular perfusion (MBG 3) post PPCI is around 3%, whereas it is approximately 29% for those with MBG<3 [87], a minimum of 1350 patients need to be randomised to demonstrate, with an alpha risk of 5% and a beta risk of 20%, a survival advantage at 1 year using thrombectomy compared with standard PCI. A metaanalysis by De Luca *et al.* [88] including 9 RCT's with 2401 patients, found that adjunctive manual thrombectomy was associated with significantly improved postprocedural TIMI3 flow (87.1% versus 81.2%, p <0.0001) and postprocedural MBG 3 (52.1% versus. 31.7%, p <0.0001), less embolisation (7.9% versus 19.5%, p <0.0001) and significant benefits in terms of 30 day mortality (1.7% versus 3.1%, p=0.04).

An individual data pooled analysis including 2686 patients from 11 trials was later reported in the ATTEMPT (Analysis of Trials on ThrombEctomy in acute Myocardial infarction based on individual PatienT data) metaanalysis [89]. At a median of 1 year follow-up, all-cause mortality, death and myocardial infarction and MACE were all significantly reduced by thrombectomy. Interestingly there was no differential effect of thrombectomy in subgroups according to diabetic status, ischaemic time, infarct-related artery or presenting TIMI flow. As expected from results of individual trials, the survival benefit observed in this metaanalysis is confined to patients treated in manual thrombectomy which emphasizes the importance of using simple rather than complex devices for thrombus removal.

The difference in effect of the type of thrombectomy device was also noted in an earlier metaanalysis of 30 studies with 6415 patients with a mean follow-up of 5 months by Bavry *et al.* [90] Among thrombus aspiration studies, mortality was 2.7% for the adjunctive device group versus 4.4% for PCI alone (p = 0.018). On the other hand, for mechanical thrombectomy, mortality was higher at 5.3% for the adjunctive device group versus 2.8% for PCI alone (p = 0.050). As for embolic protection there was no difference in mortality between the adjunctive device group (3.1%) and for PCI alone (3.4%), (p = 0.69).

None of the metanalysis incorporated the latest JETSTENT data which has indicated probable benefits of non-manual thrombectomy devices in selected subgroups of patients with larger thrombus burden and device-favourable coronary anatomy.

STENT DESIGN AND EMBOLISATION

Stent deployment often results in tissue prolapse in between stent struts. In both stable but especially more often in patients with acute coronary syndrome, the prolapsed material is often atherothrombotic material which may embolise and cause no-reflow. This phenomenon is sometimes referred to as the cheese-grater effect. The MGuard bare metal stent (Inspire-MD, Tel-Aviv, Israel) has been designed to prevent distal embolisation by containing thrombus and plaque fragments by means of a polymer mesh sleeve which is wrapped to the external surface of the struts. The effect of this embolisation protection strategy has been shown to be safe is currently being compared (in terms of achievement of a good MBG) to a strategy of conventional BMS implantation and thrombectomy in the GUARDIAN (MGuard Stent in ST-elevation Myocardial Infarction) study [91, 92]. The MASTER trial (The Safety and Efficacy Study of MGuard Stent After a Heart Attack) is another randomised study that will compare the effect of this stent to conventional BMS or drug eluting stents with ST-segment resolution as primary endpoint.

PREVENTION OF NO-REFLOW DURING PRIMARY PCI BASED ON ADDITIONAL RISK ASSESSMENT PROVIDED BY INVASIVE IMAGING DURING PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Clinical risk factors for the development of myocardial no-reflow in a patient presenting with acute myocardial infarction are well documented [5]. Age, previous coronary artery bypass surgery, a higher Killip class at presentation and a longer ischaemic time should alert treating physicians since these are amoung the most important associated factors. Angiographic characteristics with high risk of subsequent no-reflow include patency of the IRA, saphenous graft being IRA and multivessel disease. A high thrombus burden as assessed angiographically is also known to be associated with a higher risk of developing the no-reflow phenomenon [93]. Advances in imaging especially intracoronary imaging have recently helped us to better understand the pathophsiology of coronary disease even in an acute setting such as occurs in acute coronary syndromes. Moreover we can now better evaluate the implications of our invasive intervention. This additional information that can now be acquired in the modern day catheterisation lab may in the near future help us identify patients at higher risk of developing the myocardial no-reflow phenomenon which in turn will allow us to tailor treatment accordingly. By characterising coronary plaque and revealing true intraluminal atherothrombotic burden, intravascular ultrasound and optical coherence tomography have a potentially important role to play in risk stratification in the cathlab.

Table 2. Major Randomised Trials that Tested Adjunctive Thromboembolic Prevention Devices

Trial	Drug	Mode of Action	Number of Patients	Admin.	Adjunctive Treatment	Primary End-points	Microvascular Perfusion	Infarct Size	30 Day Mortality	Follow-Up	Long Term Mortality
Thiele [27]	Abciximab	Antiplatelet	154	i.c vs i.v as bolus	-	Final infarct size; microvascular obstruction extent (MRI)	1.1% vs. 3.4%, p= 0.01	15.1 % (ic) vs 23.4 % (IV) p=0.01	2.6 % vs 3.9% p=NS	30 days	NA
CICERO[28]	Abciximab	Antiplatelet	534	i.c vs i.v as bolus	Thrombus aspiration	ST resolution;	64% vs. 62% p=NS	CK 1214 vs 1746 p=0.008	1.8% vs. 2.7% p=0.526	30 days	NA
Marzilli [44]	Adenosine	Vasodilation	54	i.c		Safety and feasi-bility; TIMI flow	No-reflow in 4% vs.26% p<0.01	CK-MB 156 vs 346 p=NS	NA	NA	NA
Desmet [45]	Adenosine	Vasodilation	112	Selective i.c.	Abciximab	CMR Myocardial salvage MVO	41.3% vs. 47.8% p=0.52 5.9g vs. 2.4g p=0.07	CK-MB 224 vs 227 p=0.47	1.8% vs 3.7%	1 year	3.6% vs 3.7% p=0.97
AMISTAD II [47]	Adenosine	Vasodilation	2118	3 hour iv infusion	-	Time to first CHF or death	-	SPECT: 27% of LV vs 17% p=0.074	NA	6 months	10.3% vs 11.8 % p=0.29
Piot [57]	Cyclosporine	Myocyte preservation	58	I.V bolus	-	Infarct size as-sessed by cardiac biomarkers	-	CK (as area under the curve) 138,053 vs 247,930 (arbitrary units) p=0.04	NA	3 months	NA
Amit [49]	Nitroprusside	Vasodilation	98	i.c	-	TIMI flow; complete ST segment resolution	61.7% vs. 61.2% p=0.96	NA	NA	6 months	4.2% vs 6% p=0.68
Ito [52]	Nicorandil	K- channel opener (precise action not known)	81	i.v bolus and infusion for 24 hours followed by oral dose	-	MCE	15% vs. 33% p=0.05	NA	In-hospital: 0% vs 10%	Till dis-charge (mean 28 days)	NA
Ishii [53]	Nicorandil	K- channel opener	368	20-20 mins i.v infusion	-	Cardiovascular death; CHF	ST resolution 79.5% vs. 61.2% p= 0.0002	CK: 3076 vs 3818 p=0.03	NA	2.4 years	3.2% vs 5.5% p=0.0058

i.c. = intracoronary; i.v. – intravenous; CMR cardiac magnetic resonance imaging; MVO = microvascular obstruction. MCE= myocardial contrast echocardiography.

CORONARY PLAQUE COMPONENT AND NO-REFLOW PHENOMENON

The relationship between plaque components and no-reflow is still unclear. Gray scale intravascular ultrasound (IVUS) studies have indicated that the presence of attenuated plaque, a large plaque burden, large lipid pool and positive remodelling are risk factors for no-reflow. In 100 patients presenting with acute myocardial infarction, Tanaka *et al.* demonstrated correlation of angiographic no-reflow (13 patients) with hypercholesterolemia, fissure and dissection, lipid pool-like IVUS image, lesion, and reference external elastic membrane cross-sectional area [94]. Multivariate logistic regression analysis showed that lipid pool-like image ($P<0.05$; odds ratio 118; 95% CI, 1.28 to 11 008) and lesion elastic membrane cross-sectional area ($P<0.05$; odds ratio

1.55; 95% CI 1.01 to 2.38) were independent predictive factors of no-reflow phenomenon after reperfusion for acute myocardial infarction.

IVUS virtual histology (VH) which allows spectral analysis of IVUS radiofrequency data and therefore quantifies tissue characterization has also been employed to study the ability of plaque characterisation in predicting no-reflow. Color coding and plaque burden can stratify plaque types into four major types, namely fibro-fatty, dense calcium, and necrotic core (NC). Thin-cap fibroatheroma (TCFA) with this methodology is often defined as focal, NC-rich (>/=10% of the cross-sectional area) plaques being in contact with the lumen in a plaque burden >/=40%. A higher necrotic core burden as opposed to fibrous content, has been associated with a higher risk of no-reflow [95, 96]. Hong *et al.* retrospectively analysed 190 consecutive patients presenting with acute coronary syndrome (24% STEMI, 7%NSTEMI and 58% unstable angina) who were imaged using IVUS-VH and subsequent stent implantation [95]. No-reflow was observed in 24 patients (12.6%) post-stenting. The absolute and percentage NC areas at the minimum lumen sites (1.6 +/- 1.2 versus 0.9 +/- 0.8 mm(2), P < 0.001, and 24.5 +/- 14.3 versus 16.1 +/- 10.6%, P = 0.001, respectively) and the absolute and %NC volumes (30 +/- 24 versus 16 +/- 17 mm(3), P = 0.001, and 22 +/- 11 versus 14 +/- 8%, P < 0.001, respectively) were significantly greater, and the presence of at least one TCFA and multiple TCFAs within culprit lesions (71 versus 36%, P = 0.001, and 38 versus 15%, P = 0.005, respectively) was significantly more common in the no-reflow group. The %NC volume was the only independent predictor of no-reflow (odds ratio = 1.126; 95% CI 1.045-1.214, P = 0.002). These studies suggests that novel intravascular imaging may identify patients who are at risk but perhaps more importantly it may imply that treatment pre-stenting that induces a favourable change in the plaque composition, has the potential to prevent no-reflow once stenting is deemed necessary. In this context an observational study showed that STEMI patients with chronic statin pre-treatment had a lower incidence of no-reflow [14].

In contrast 'marble-like' images on IVUS VH, consistent with a large fibro-fatty and fibrous content (plaque volume of fibro-fatty + fibrous >80% and containing fibro-fatty plaque volume >10%) were associated with angiographic no-reflow in a small study with 50 patients with MI, eight of whom had no-reflow [97]. Corrected TIMI frame counts of the cases with "marble-like" image were significantly larger than the cases without it (46.8 +/- 5.6 versus 27.4 +/- 2.3, P = 0.01). Both large plaque burden as well as large external elastic membrane volume were both higher in the no-reflow group as in previous studies.

In a similar small study in which 12 of 57 patients developed no-reflow, fibrofatty volume over the entire lesion length was again the only independent factor (beta = 0.359, 95% confidence interval 0.002 to 0.012, p = 0.006) for slow flow during PPCI [98].

The discrepancy in VH results may be in part due to the different classifications as well as suboptimal interpretation and reproducibility of the intravascular imaging techniques with the methods currently available. The use of near Infrared spectroscopy to determine the lipid content of the culprit lesion may help to identify plaques with an increased risk of embolisation after stent implantation through the cheesegrater effect [99]. Such novel developments and improvements in intracoronary tissue/plaque characterisation may in the future play a crucial role in identifying cases at high risk of no-reflow after stenting and therefore help device strategies to prevent this phenomenon.

CONCLUSION

The no-reflow phenomenon remains a difficult therapeutic target in modern day medicine. Efforts to reduce the negative impact that myocardial infarction has on the patient's morbidity and mortality should start by a better understanding of the pathophysiological cascade involved. Prevention with timely intervention, by both pharmacological and mechanical means, to reduce the extent of damage to the myocardium should be the primary focus in the management of patients suffering an acute myocardial infarction. While GP IIb/IIIa inhibitors and manual thrombectomy devices have been shown to improve myocardial perfusion, additional innovative therapies are needed. Novel preventive measures should be able to demonstrate a reduction in incidence of the no-reflow phenomenon that would translate in prognostic benefits for the patient.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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5.4

Impact of Multiple Balloon Inflations during Primary Percutaneous Coronary Intervention on Infarct Size and Long-Term Clinical Outcome in ST-Segment Elevation Myocardial Infarction: Real-World Postconditioning.

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Impact of multiple balloon inflations during primary percutaneous coronary intervention on infarct size and long-term clinical outcomes in ST-segment elevation myocardial infarction: real-world postconditioning

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Abstract Interrupting myocardial reperfusion with intermittent episodes of ischemia (i.e., postconditioning) during primary percutaneous coronary intervention (PPCI) has been suggested to protect myocardium in ST-segment elevation myocardial infarction (STEMI). Nevertheless, trials provide inconsistent results and any advantage in long-term outcomes remains elusive. Using a retrospective study design, we evaluated the impact of balloon inflations during PPCI on enzymatic infarct size (IS) and long-term outcomes. We included 634 first-time STEMI patients undergoing PPCI with an occluded infarct-related artery and adequate reperfusion thereafter and divided these into: patients receiving 1–3 inflations in the infarct-related artery [considered minimum for patency/stent placement (controls); $n = 398$] versus ≥ 4 [average cycles in clinical protocols (postconditioning analogue); $n = 236$]. IS, assessed by peak creatine kinase, was lower in the postconditioning analogue group compared with controls [median (interquartile range) 1,287 (770–2,498) vs. 1,626 (811–3,057) UI/L; $p = 0.02$], corresponding to a 21 % IS reduction. This effect may be more pronounced in women, patients without diabetes/hypercholesterolemia, patients presenting within 3–6 h or with first balloon re-occlusion ≤ 1 min. No differences were observed in 4-year mortality or MACCE between groups. Four or more inflations during PPCI reduced enzymatic IS in STEMI patients under well-defined conditions, but did not translate into improved long-term outcomes in the present study. Large-scale randomized trials following strict postconditioning protocols are needed to clarify this effect.

Keywords Postconditioning · Primary percutaneous coronary intervention · Reperfusion injury · ST-segment elevation myocardial infarction

Abbreviations

CK	Creatine kinase
IPOC	Ischemic postconditioning
IRA	Infarct-related artery
IS	Infarct size
LAD	Left anterior descending coronary artery
MACCE	Major adverse cardiac and cerebrovascular events
PPCI	Primary percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction

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Introduction

In patients presenting with ST-segment elevation myocardial infarction (STEMI), infarct size (IS) can be limited by early myocardial reperfusion via primary percutaneous coronary intervention (PPCI), thereby preserving left

ventricular systolic function and improving clinical outcome. However, the full benefits of myocardial reperfusion are not realized, given that the process of restoring blood flow to the ischemic myocardium can independently induce cell death (i.e., lethal reperfusion injury) [13]. Hence, cardioprotective strategies that potentially modify the conditions of reperfusion and limit reperfusion injury are of major clinical interest.

Ischemic postconditioning (IPOC) is an interventional strategy in which controlled, brief, intermittent episodes of re-occlusions in the first few minutes of reperfusion can protect myocardium from lethal reperfusion injury [28]. The concept of interrupting the myocardial reperfusion process with the angioplasty balloon to reduce myocardial IS (as assessed by different modalities, including cardiac biomarkers) has been demonstrated to be efficacious in several small-size studies evaluating STEMI patients undergoing PPCI [10, 19, 21, 26]. However, recent trials provide inconsistent results [4–6, 18, 20]. The efficacy of IPOC appears to be hampered by various confounders and additionally, uncertainties remain about the optimal protective IPOC protocol [12]. More importantly, the effect of IPOC on long-term clinical endpoints such as mortality or major adverse cardiac and cerebrovascular events (MACCE) remains unknown.

In the absence of adequately powered clinical trials, we aimed to investigate the impact of multiple balloon inflations during PPCI on enzymatic IS in patients with STEMI. Accordingly, we aimed to determine whether this may have served as a real-world analogue for IPOC. Secondly, to assess potential confounders, we evaluated whether these effects differed in prespecified subgroups. Finally, we examined the impact of balloon inflations during PPCI on long-term clinical outcome.

Methods

Study design and population

As the principal regional cardiac referral center, an ongoing registry of catheter-based coronary procedures is maintained in an electronic database at our institution. We conducted a retrospective chart review, together with the electronic medical records, of all patients who presented to our institution between June 2006 and June 2010 with STEMI undergoing PPCI. We included patients if they: were $\geq$18 years of age; had symptoms suggesting acute myocardial ischemia lasting >30 min and ST-segment elevation >0.1 mV in $\geq$2 contiguous leads; had an occluded infarct-related artery (IRA) with TIMI-0/1 flow on initial angiogram; had adequate reperfusion after PCI (TIMI-3). We excluded patients with previous myocardial infarction or CABG, cardiogenic shock, cardiac arrest or thrombectomy. The current retrospective study design was modeled after the study by Darling and colleagues [3].

Ethics

Patients were not subject to acts for the purpose of this retrospective study. Neither was any mode of behavior imposed, otherwise than their regular treatment. Therefore, according to Dutch law, written informed consent for a patient to be enrolled in this study was not required. This study was conducted according to the Erasmus MC Privacy Policy and regulations for the appropriate use of data in patient oriented research and was approved by the institutional ethics committee.

Procedures and medications

All procedures were performed following standard procedural guidelines at the time. Intraprocedural anticoagulation was ensured using unfractionated heparin (to achieve an activated clotting time >250 s in all patients). All patients received an aspirin loading dose of 300 mg and were encouraged to continue this regimen indefinitely. After a 600 mg clopidogrel loading dose, additional antiplatelet therapy with a 75 mg clopidogrel maintenance dose was instituted in all patients, who were then advised to continue this regimen for 12 months. In all cases, the interventional strategy, including pre-dilatation, post-dilatation, glycoprotein IIb/IIIa inhibitors (to prevent or to treat distal microembolization) and other medications such as adenosine, was at the discretion of the interventional cardiologist.

Balloon inflations

In the currently available clinical trials, the IPOC protocols consisted of 2–4 cycles of ischemia and reperfusion (produced by inflations/deflations of angioplasty balloon) after direct stenting [27]. Taking into account an average of three cycles utilized in the clinical protocols plus one balloon inflation for direct stenting, we reasoned that $\geq$4 inflations would mimic an IPOC stimulus in a real-world setting. Thus, the study population was divided into patients receiving 1–3 balloon inflations during PPCI in the IRA (considered minimum range for achieving patency/stent placement [controls]) and patients receiving $\geq$4 (analogue for IPOC). The definition of study population by Darling et al. [3] served as a model for the current description. The number of balloon inflations, the average duration of inflations and the delay between first and second inflation during PPCI were obtained from our catheterization laboratory's procedure database. In this electronic database, each balloon inflation and its location and duration in the coronary artery tree during the

procedure is immediately registered, by a cathlab technician using an angioplasty timer, upon indication by the interventional cardiologist. The delay of first re-occlusion after reflow was defined as the time period between first and second balloon inflation. Clinical indications for multiple balloon inflations in the IRA were: long or multiple lesions requiring >1 pre-dilatation, the placement of ≥2 stents or the need for >1 post-dilatation.

Study endpoints and follow-up

The primary study endpoint was enzymatic IS assessed by peak CK release and was defined as the highest serum concentration in the 72-h time period after the intervention. The upper limit of normal was 180 U/L. The secondary clinical endpoints included all-cause mortality and MACCE during 4-year follow-up. MACCE was defined as a composite of all-cause mortality, non-fatal myocardial infarction, PCI, CABG or stroke. Survival data for all patients were obtained from municipal civil registries. A questionnaire was subsequently sent to all living patients with specific questions on rehospitalization for MACCE. For patients who suffered an adverse event at another centre, medical records or discharge letters from the other institutions were systematically reviewed.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on normal distribution and were compared using the Student *t* test or Mann–Whitney *U* test as appropriate. Categorical variables are presented as percentages and were compared using the Chi-square test. Univariable and multivariable linear regression analyses were performed to evaluate the relationship between number of balloon inflations with peak CK after logarithmic transformation. In multivariable analyses the variables age, gender, diabetes, number of diseased vessels, symptom-to-balloon time, Rentrop collateral grade, proximal occlusion of either left anterior descending (LAD) or right coronary artery (RCA) and number of balloon inflations were entered into the model. The differences of median peak CK with 95 % confidence intervals (CI) in subgroups were estimated using the Hodges–Lehmann method for the location shift according to the following prespecified variables: gender, age, diabetes, hypercholesterolemia, hypertension, collaterals, vessel disease, culprit artery, delay first re-occlusion, and symptom-to-balloon time. Patients lost to follow-up were considered at risk until the date of last contact, at which time-point they were censored. Clinical outcomes are presented as Kaplan–Meier survival estimates and were compared using the log-rank test. Multivariable Cox proportional hazard regression analyses were performed to evaluate the relationship between number of balloon inflations and all-cause mortality and MACCE, and are presented as unadjusted and adjusted hazard ratios (HR) with associated 95 % CIs.

The Hodges–Lehmann analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). All other statistical analyses were performed using SPSS version 20 (SPSS, Inc., Chicago, Illinois, USA). All statistical tests were two-tailed and a $p < 0.05$ was considered to indicate statistical significance.

Results

Patient characteristics

Between June 2006 and June 2010 a total of 2,520 STEMI patients presented to our institution for PPCI, of which 1,086 met the eligibility criteria. Of these, patients without available cardiac enzymes ($n = 306$) and patients without available balloon inflation data ($n = 146$) were excluded. Thus, the current analysis included 634 patients ($n = 398$ in the control group and $n = 236$ in the IPOC analogue group) (Fig. 1). Baseline, angiographic, and procedural characteristics are listed in Table 1. Patients in the IPOC

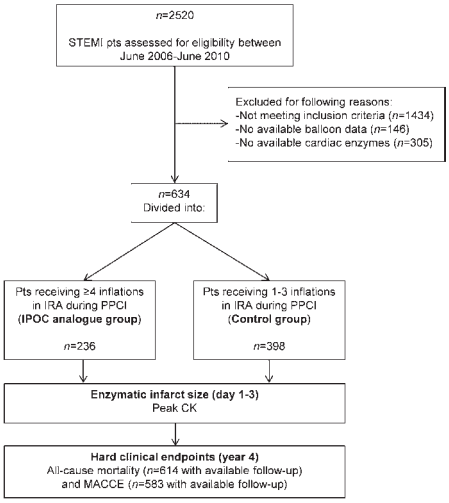

Fig. 1 Study flow diagram. *CK* creatine kinase, *IPOC* ischemic postconditioning, *IRA* infarct-related artery, *MACCE* major adverse cardiac and cerebrovascular events, *PPCI* primary percutaneous coronary intervention, *STEMI* ST-segment elevation myocardial infarction

Table 1 Baseline, angiographic, and procedural characteristics

Variables	Control group ($n = 398$)[a]	IPOC analogue group ($n = 236$)[b]	p value
Clinical characteristics and risk factors			
Age (years)	59.9 ± 13.0	62.8 ± 12.6	0.006
Male	75.1	71.6	0.33
Hypertension	38.4	41.0	0.51
Diabetes	10.3	9.7	0.82
Hypercholesterolemia	34.4	36.1	0.67
Current smoker	49.0	39.8	0.03
Family history	35.6	36.3	0.86
Angiographic and procedural characteristics			
Infarct-related artery			
LAD	40.7	36.9	0.34
LCx	17.8	16.1	0.58
RCA	41.5	47.0	0.17
No. of diseased vessels			
1	64.1	44.5	<0.001
2	19.6	30.5	0.002
3	14.6	19.1	0.14
Left main, any[c]	1.8	5.9	0.005
Collaterals			
Rentrop flow grade 0	81.4	77.7	0.27
Rentrop flow grade 1	11.7	10.0	0.52
Rentrop flow grade 2	5.4	8.3	0.15
Rentrop flow grade 3	1.5	3.9	0.06
TIMI flow in culprit artery before PCI			
TIMI 0	88.9	89.4	0.86
TIMI 1	11.1	10.6	0.86
Symptom onset-to-balloon time			
≤3 h	41.3	35.7	0.19
3–6 h	39.7	39.5	0.97
6–12 h	14.4	17.1	0.38
>12 h[e]	4.6	7.6	0.14
Symptom onset-to-balloon time (h)	3.3 (2.4–5.1)	3.8 (2.4–5.9)	0.19
Glycoprotein IIb/IIIa inhibitor use	30.2	36.0	0.13
Adenosine use	0.5	0.8	0.60
Balloon inflation data			
Average balloon inflation time (s)	11.7 (9.5–15.0)	11.6 (9.7–15.7)	0.49
Average balloon inflation pressure (atm)	16.0 (14.0–19.3)	15.0 (12.8–17.0)	<0.001
Delay 1st re-occlusion after reflow (min)	4.0 (2.0–7.0)	3.0 (1.0–6.0)	0.03
Medication during hospitalization in interventional centre[d]			
Aspirin	99.7	100	0.44
Thienopyridine	100	100	–
ACE-i/ARB	3.8	5.0	0.48
β-blocker	50.9	48.6	0.59
Statin	85.1	86.3	0.69
Calcium channel blocker	5.7	7.3	0.44
Diuretic	1.1	1.4	0.76
Nitrate	24.4	25.0	0.87

Data are presented as %, mean (SD) or median (IQR)

MACCE major adverse cardiac events, *ACE-i/ARB* angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, *LAD* left anterior descending coronary artery, *LCx* left circumflex coronary artery, *PCI* percutaneous coronary intervention, *RCA* right coronary artery, *TIMI* thrombolysis in myocardial infarction

[a] Patients receiving 1–3 balloon inflations

[b] Patients receiving ≥4 balloon inflations

[c] Left main only or in combination with 1-, 2- or 3-vessel disease

[d] Percentages upon transfer to peripheral hospital after percutaneous coronary intervention

[e] For patients with ischemic times >12 h, median symptom onset-to-balloon time (with interquartile range) was 16.1 h (13.1–21.5) in the control group ($n = 17$) and 16.5 h (14.1–21.6) in the IPOC analogue group ($n = 16$)

analogue group were older, were less frequently smokers, had less single-vessel and more multivessel disease, and had a tendency of having more Rentrop grade 3 collaterals compared to controls.

Balloon inflation data

The patients in the IPOC analogue group received a median of 5 balloon inflations during PPCI, compared with 2 inflations in controls ($p < 0.0001$) (Fig. 2a). The balloon inflation time and pressure in the IPOC analogue group were 11.6 s (9.7–15.7) and 15.0 atm (12.8–17.0), compared to 11.7 s (9.5–15.0) ($p = 0.49$) and 16.0 atm (14.0–19.3) ($p < 0.001$) in the control group, respectively.

The delay of first re-occlusion was 3.0 min (1.0–6.0) in the IPOC analogue group, compared to 4.0 min (2.0–7.0) in controls ($p = 0.03$) (Table 1).

Infarct size

Peak CK release was significantly lower in the IPOC analogue group compared with controls [1,287 (770–2,498) vs. 1,626 (811–3,057) UI/L; $p = 0.02$] (Fig. 2b). The lower peak CK values in the IPOC analogue group appeared to be more pronounced in: women, patients without diabetes or hypercholesterolemia, patients presenting within 3–6 h of symptom onset, and patients with delay of first re-occlusion ≤1 min (Fig. 2c).

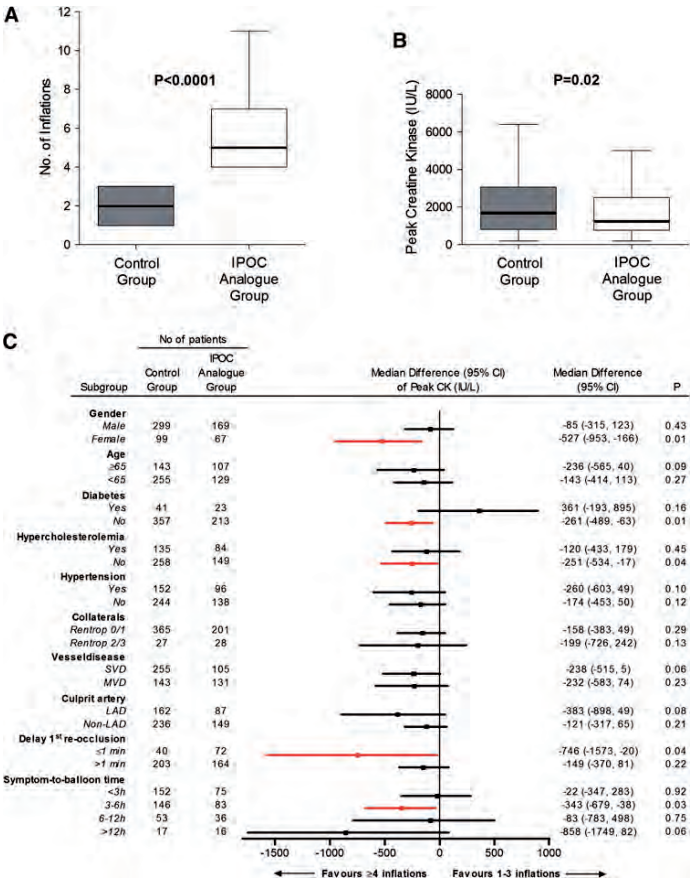

Fig. 2 Balloon inflations and enzymatic infarct size. Number of inflations (**a**), peak creatine kinase release in the postconditioning analogue group versus controls in the overall study group (**b**) and differences of median peak enzyme release with 95 % confidence intervals between study groups according to relevant patient subgroups (**c**). The reference for the difference is 1–3 inflations, thus, a negative difference indicates a lower peak creatine kinase in those with ≥4 inflations (**c**). *CI* confidence interval, *CK* creatine kinase, *IPOC* ischemic postconditioning, *LAD* left anterior descending, *MVD* multivessel disease, *SVD* single-vessel disease

Table 2 Impact of balloon inflations on long-term clinical outcomes

	Unadjusted			Adjusted		
	Hazard ratio	95 % CI	*p*	Hazard ratio[a]	95 % CI	*p*
Mortality	1.21	0.69, 2.11	0.50	0.86	0.44, 1.67	0.65
MACCE	1.22	0.83, 1.79	0.31	0.87	0.57, 1.33	0.52

CI confidence interval, *MACCE* major adverse cardiac and cerebrovascular events

[a] The multivariable Cox-regression model included age, gender, diabetes, number of diseased vessels, symptom-to-balloon time, Rentrop collateral grade, proximal occlusion of either left anterior descending (LAD) or right coronary artery (RCA) and number of balloon inflations

Long-term outcomes

Clinical follow-up for mortality was available for 614 patients (97 %). There were 51 deaths during the follow-up: 21 deaths occurred in the IPOC analogue group and 30 deaths occurred in the control group (Kaplan–Meier estimates of 4-year mortality of 10.0 and 9.0 %, respectively; adjusted HR 0.86, 95 % CI 0.44–1.67; $p = 0.65$). Clinical follow-up for MACCE was available for 583 patients (92 %). There were 108 MACCEs during the follow-up: 44 events occurred in the IPOC analogue group and 64 events occurred in the control group (Kaplan–Meier estimates of 4-year MACCE of 24.8 and 26.8 %, respectively; adjusted HR 0.87, 95 % CI 0.57–1.33; $p = 0.52$) (Table 2; Fig. 3).

Discussion

The present analysis showed that STEMI patients receiving $\geq$4 balloon inflations during PPCI displayed lower peak CK values compared with patients receiving 1–3 inflations, corresponding to an enzymatic IS reduction of 21 %. This finding adds further credence to the concept that interrupting the reperfusion procedure with several intermittent episodes of re-occlusions (produced by inflations of the angioplasty balloon) may have acted as a real-world analogue for IPOC and thereby attenuated reperfusion injury. Although the overall beneficial effect remained similar, the lower peak CK values in the IPOC analogue group may be more pronounced in women, patients without diabetes or hypercholesterolemia, patients presenting within 3–6 h of symptom onset and patients with a delay of first re-occlusion $\leq$1 min. There were no differences in the rates of mortality or MACCE during 4-year follow-up between the IPOC analogue group and the control group in the current study.

Previous studies

Although it has been demonstrated that IPOC reduced IS with [19, 21, 26] or without [9] an improvement in left ventricular function in the clinical setting, not all studies have been positive [4, 5, 18, 20]. Recently, it was reported that IPOC was not able to reduce IS or improve left ventricular function (assessed by cardiac magnetic resonance imaging) in 79 first-time STEMI patients presenting for PPCI within 12 h of symptom onset [5]. Likewise, Tarantini et al. [20] failed to demonstrate any advantage of IPOC in terms of IS reduction assessed by cardiac magnetic resonance or myocardial reperfusion markers. However, in this trial, the proportion of diabetics was not balanced between study groups (18 % in IPOC group vs. 3 % in controls; $p = 0.056$), which may have blunted the effects of IPOC. Also, it may well be that in patients with symptom-to-balloon times <12 h, a specific IPOC protocol may be ineffective. Importantly, the eligibility criteria differed substantially in the currently available clinical IPOC trials, along with the defined study endpoints [27]. Of these, serum CK release is the most widely used study

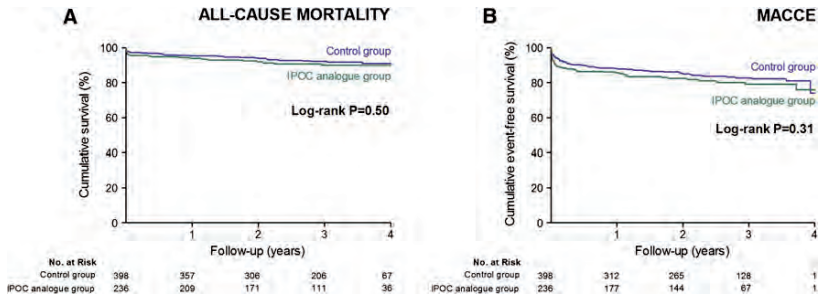

Fig. 3 Kaplan–Meier curves of 4-year mortality and major adverse cardiac and cerebrovascular events

endpoint [8] and peak CK values strongly correlate with IS and predict cardiac outcomes in STEMI patients treated with PPCI [2, 7]. Currently, no biomarker exists that confirms whether a specific IPOC protocol induced a "post-conditioned" state [24]. Nevertheless, assessment of myocardial damage after STEMI is crucial in evaluating the efficacy of reperfusion therapy and predicting prognosis. For instance, most recently Hahn et al. [6] failed to demonstrate any advantage of IPOC in terms of reperfusion markers as assessed by complete ST-segment resolution (>70 %) 30 min post-PCI and postprocedural TIMI flow or myocardial blush grade in a large randomized trial involving 700 STEMI patients. The current results are in line with previous randomized studies, in which IPOC resulted in IS reduction ranging from 27 to 40 % as measured by CK release [19, 21, 23, 26]. The current results are also in agreement with two retrospective studies involving 115 and 85 STEMI patients in which ≥4 [3] or ≥3 [25] balloon inflations during PPCI were associated with lower peak CK values compared with 1–3 or 1–2 inflations. The present study extends these observations by assessing potential confounders and evaluating the association between balloon inflations and long-term clinical outcomes after PPCI in a large cohort of 634 patients. Still, important differences remain with the aforementioned (positive and negative) randomized trials when considering the major determinants of IS. The current study included a proportion of patients with collateral circulation, patients with a wide range of ischemic times, and patients with both LAD and non-LAD infarctions (the latter representing usually smaller areas at risk). In this regard it is noteworthy that the exclusion of patients with Rentrop 2/3 collateral grades ($n = 55$) from the study cohort did not change the beneficial effect of ≥4 balloon inflations during PPCI on enzymatic IS in the IPOC analogue group compared with controls ($p = 0.04$). In addition, we adjusted for these determinants in the regression analysis, including the influence of collateral score.

Long-term clinical outcomes

The beneficial effect of ≥4 balloon inflations during PPCI on peak CK release in the current study did not translate into improved 4-year clinical outcomes. The reasons for these observations could be related to a number of factors. First, multivessel disease was more often encountered among patients in the IPOC analogue group compared with controls. Consequently, these patients were more likely to receive staged procedures for repeat revascularizations. Second, reperfusion therapy (PCI and thrombolysis) has already reduced mortality after acute myocardial infarction to low levels (4–6 %) [1], making further significant reductions by adjunctive therapies difficult to achieve. In fact, IS may not impact outcomes such as mortality until a threshold IS is achieved. In the current study, IS (peak CK values of 1,287 vs. 1,626 UI/L in study groups) was smaller compared to earlier retrospective studies (1,655 vs. 2,272 UI/L [3]; 2,056 vs. 2,603 UI/L [25]). With the relatively small overall IS and current mortality rates, the present study was likely to be underpowered to discern differences in all-cause mortality. Therefore, no definite conclusions can be drawn regarding the impact of IPOC on long-term outcomes. This is especially true, when considering that most recently both remote ischemic pre- [22] and perconditioning [17] have been found to improve long-term outcomes in prospective randomized trials, including all-cause mortality, in the setting of CABG and STEMI, respectively. Nevertheless, it is reassuring to observe no excess clinical events in the IPOC analogue group in the present study.

IPOC mechanisms and potential confounders

The current mechanistic paradigm for IPOC invokes the activation of signal transduction pathways by autacoid triggers, which accumulate extracellularly in response to the IPOC stimulus and act on their cell surface receptors or other molecular targets. Ultimately, signaling pathways activated by IPOC probably converge on mitochondria to inhibit the opening of the mitochondrial permeability transition pore, thereby preventing myocardial cell death [12]. Many of these cellular signaling elements might be affected by confounders, co-morbidities or co-medication, as these conditions are associated with fundamental molecular alterations potentially affecting responses to IPOC [12]. Currently, there is insufficient information to judge how and to what extent several confounding factors, including cardiovascular risk factors, gender, and age influence IPOC efficacy in the clinical setting. In this light, we investigated the effect of ≥4 balloon inflations (as a real-world analogue for IPOC) compared with controls in various predefined subgroups. Patients in the IPOC analogue group displayed lower peak CK values compared with controls in nearly all subgroups with a possibly more pronounced effect in women and patients without diabetes or hypercholesterolemia, among others (Fig. 2c). At present, there is no strong evidence whether IPOC-induced protection is gender-dependent [12]. Nevertheless, the current observation is not consistent with a recent meta-analysis in which a pronounced cardioprotective effect of IPOC in male patients was reported [29]. Conversely, although statistically not significant ($p = 0.16$), patients with diabetes displayed higher peak CK concentrations in the IPOC analogue group. This finding is compatible with

observations from the pre-clinical setting, in which IPOC-induced cardioprotection was shown to be impaired in diabetes: the IS-limiting effect was lost or required extra cycles of ischemia/reperfusion in various animal models of diabetes [11].

IPOC protocol and protection

There is consensus that the delay in applying the first re-occlusion after reflow must be relatively short (<1 min) for exerting the beneficial effects of IPOC [24]. In the present study, there was a significant beneficial effect in the IPOC analogue group when this delay was indeed within 1 min, whereas delaying the first re-occlusion above 1 min lowered the efficiency (Fig. 2c). In this regard, one practical issue potentially interfering with IPOC is the use of manual aspiration thrombectomy. This technique usually re-establishes a significant blood flow in the IRA and the delay between applying the procedure and initiating the IPOC protocol might exceed the very short time frame in which IPOC has been shown to be efficient. For this reason, we excluded patients receiving thrombectomy from the present analysis. In the current study, median delay of first re-occlusion after reflow was 3.0 min in the IPOC analogue group. In contrast, in the excluded thrombectomy patients ($n = 130$), median delay was 6.7 min. Indeed, when performing a sensitivity analysis by including the thrombectomy cohort into the current study, median delay of first re-occlusion became 4.0 min in the IPOC analogue group (and even 8.0 min in patients receiving thrombectomy in the IPOC analogue group). Additionally, the beneficial effect of ≥4 balloon inflations during PPCI on enzymatic IS in the IPOC analogue group ($n = 484$) compared to controls ($n = 280$) lost its statistical significance [median peak CK (interquartile range) 1,429 (790–2,761) vs. 1,637 (802–3,114) UI/L; $p = 0.09$] when including the thrombectomy cohort. Future studies need to explore this issue in a randomized setting. On the other hand, despite a median first re-occlusion delay of 3 min (1.0–6.0) in the IPOC analogue group, the use of ≥4 inflations was still associated with lower peak CK values. This observation is in agreement with recent findings in which delaying the IPOC stimulus >1 min after reperfusion onset did not abrogate cardioprotection in the in vivo mouse heart [15] and may suggest that IPOC >1 min may still confer cardioprotection in a clinical setting. Nevertheless, the optimal time window for application of IPOC remains to be determined.

At present, uncertainties remain about the most effective IPOC algorithm in the clinical setting, including number and duration of re-occlusions [24]. In an attempt to define the optimal algorithm in the current cohort, we compared patients receiving a single balloon inflation with the multiple inflation groups. We were not able to ascertain that one particular inflation group was significantly associated with reduced peak CK values (data not shown).

A similar predicament also exists regarding the total duration of the index ischemia. A certain IPOC algorithm applied after an index ischemia of 30 or 45 min significantly reduced IS, but not after an index ischemia of 60 min or longer in a pre-clinical model [16]. Also, with too brief index ischemia, IPOC failed to reduce IS [14]. Hence, there is a need to define the optimal protective protocol for a given duration of the index ischemia. In the current analysis, patients presenting within 3–6 h may have accrued the greatest benefit in the IPOC analogue group. Surprisingly, patients with short ischemic times (<3 h) and those presenting more than 12 h following symptom onset also favored ≥4 balloon inflations. This observation might be especially important as the relationship between extent of myocardial reperfusion injury and very short or very long ischemic times have not been fully elucidated.

Limitations

The current study suffers from inherent limitations of a non-randomized trial and thus should be considered as a hypothesis-generating post hoc analysis. There were significant differences between study groups in terms of baseline characteristics. To compensate for these differences, we have performed adjustments employing regression and multivariate analyses. PPCI procedures in routine practice were unable to mimic a strict IPOC protocol utilized in randomized trials. Hence, we do not consider ≥4 balloon inflations during PPCI as a surrogate for IPOC. Nonetheless, we limited our analysis to those patients exhibiting a fully occluded IRA and a postprocedural TIMI-3 flow, both representing essential conditions for therapeutic application of IPOC, and were able to demonstrate a beneficial effect on enzymatic IS. Accordingly, our data underscore the need for further prospective studies. We were unable to directly quantify the area at risk in the study population due to the retrospective study design. In an attempt to adjust for (relatively) large volumes at risk, we corrected for proximal LAD or RCA infarctions. The possibility remains that true peak enzyme values were missed. Nevertheless, blood sampling as performed in this study reflects routine clinical practice. Although we did not collect the exact time points of the measurements, we used the highest biomarker concentration in the 72-h time period post-intervention. We were unable to report on co-medication of patients with pre-existing risk factors at the time of presentation, as certain pharmacological agents (e.g., angiotensin-converting enzyme inhibitors) have been shown to impact on IS reduction by IPOC in animal models

[12]. However, we reported the prescription rates of pharmacological therapies during hospitalization which was not different between groups, possibly reflecting their chronic use. Moreover, by performing subgroup analyses, we provided insight into the efficacy of multiple balloon inflations in the absence or presence of cardiovascular risk factors. Despite the large number of patients in the current study ($n = 634$) and 97 % available 4-year follow-up, only 51 deaths occurred. This low mortality rate likely reflects the relatively small infarct sizes in our study population. The latter may, in turn be a consequence of not limiting the analysis to patients with proximal lesions (associated with larger volumes at risk). We were unable to report on cardiac death, and the potential misclassification by the use of all-cause mortality in the composite MACCE may have resulted in an underestimation of the relationship between $\geq$4 balloon inflations during PPCI and outcome. More importantly, an a priori power analysis was not conducted due to the retrospective nature of the study, and with the generally small infarcts and low mortality rates, the present study likely lacks the statistical power to discern differences in all-cause mortality.

Conclusion

The present study suggests that the use of $\geq$4 balloon inflations during PPCI reduces enzymatic IS in patients with STEMI under well-defined conditions. This effect may be more pronounced in women, patients without diabetes or hypercholesterolemia, those presenting within 3–6 h, and those with first re-occlusion delay $\leq$1 min. This hypothesis-generating study suggests that $\geq$4 inflations during PPCI may have served as a real-world IPOC stimulus and possibly may reflect the phenomenon's potential in routine clinical practice. Although we present unique data concerning long-term clinical outcomes, adequately powered randomized trials are necessary with strict adherence to IPOC protocol to determine whether a reduction in IS by IPOC translates into improved clinical outcomes.

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Conflict of interest None declared.

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5.5

Comparison of six-year clinical outcome of sirolimus- and paclitaxel-eluting stents to bare-metal stents in patients with ST-segment elevation myocardial infarction: an analysis of the RESEARCH (rapamycin-eluting stent evaluated at Rotterdam cardiology hospital) and T-SEARCH (taxus stent evaluated at Rotterdam cardiology hospital) registries.

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Comparison of Six-Year Clinical Outcome of Sirolimus- and Paclitaxel-Eluting Stents to Bare-Metal Stents in Patients with ST-Segment Elevation Myocardial Infarction: An Analysis of the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus Stent Evaluated at Rotterdam Cardiology Hospital) Registries

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ABSTRACT: Background. Short- and long-term data showed that drug-eluting stents (DES) significantly decreased target vessel revascularization (TVR) and major adverse cardiac event (MACE) rates compared to bare-metal stents (BMS). However, conflicting long-term data remain for patients with ST-segment elevation myocardial infarction (STEMI). **Objective.** Our aim was to assess the 6-year clinical outcome of all patients undergoing primary percutaneous coronary intervention (PPCI) for a de novo lesion with exclusive use of BMS, sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES). **Methods.** Three PPCI cohorts (BMS = 80; SES = 92; PES = 162) were systematically followed for the occurrence of MACE. Results. Very late stent thrombosis was more common after the implantation of SES as compared to PES or BMS (7.6%, 0.6%, and 0.0%, respectively; p = 0.001). Kaplan-Meier estimates indicate no statistically significant difference for mortality between the three stent types at 6 years (BMS = 25%; SES = 15%; PES = 21%; Log-rank p = 0.2). After adjustment for differences in baseline characteristics, mortality, mortality/myocardial infarction (MI), and MACE rates were significantly lower for SES compared to BMS, but not for PES (aHR = 0.41, 95% CI: 0.17–0.98; aHR = 0.44, 95% CI: 0.21–0.96; aHR = 0.35, 95% CI: 0.17–0.72, respectively). No differences were observed between the three stent types for TVR rates. Conclusion. Neither SES nor PES improved safety or efficacy as compared to BMS in a STEMI population at 6 years. After adjusting, the usage of SES resulted in a significant decrease in mortality, mortality/MI and MACE rates as compared to BMS, in contrast to the usage of PES. SES and PES have a similar effectiveness and safety profile, although very late stent thrombosis was more common with SES.

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The urgent restoration of blood flow to the culprit coronary artery is vital after a sudden thrombotic obstruction causes a myocardial infarction with ST-segment elevations on the electrocardiogram. The duration and location of the coronary obstruction and the existence of collateral vessels to the affected myocardial region are the main factors affecting the size of myocardial necrosis and eventually the prognosis of these patients.

Although the implantation of drug-eluting stents (DES) effectively reduces restenosis rates in various subsets of patient groups including "real-world" patients compared to bare-metal stents (BMS), there still remains considerable uncertainty for the implantation of DES in a primary percutaneous coronary intervention (PPCI) setting due to contrary findings on efficacy and safety endpoints.[1–5] In particular, the potential of more very late stent thrombosis after DES implantation, which could be even more pronounced in this high-risk patient population with vulnerable coronary artery disease (CAD), caused a serious dilemma.[6–11]

A recent meta-analysis, consisting of 13 randomized trials, showed that ST-segment elevation myocardial infarction (STEMI) patients treated with a DES had fewer target vessel revascularization (TVR) procedures as compared with those treated with a BMS in the first year post-PCI without any significant differences in cardiac mortality and stent thrombosis rates.[12] In contrast, our 3- and 4-year follow-up data of relatively small consecutive patient cohorts suggested that neither sirolimus-eluting stents (SES) nor paclitaxel-eluting stents (PES) were superior to BMS in terms of decreasing mortality, TVR and major adverse cardiac event (MACE) rates in PPCI patients.[13,14] As a consequence of the paucity of long-term data combined with concerns of the increased occurrence of stent thrombosis later than 1 year after DES implantation, we evaluated the 6-year clinical outcomes of STEMI patients treated with BMS and DES in our academic center.

Methods

Patient population and study design. A total of 334 consecutive STEMI patients were treated with PPCI for de

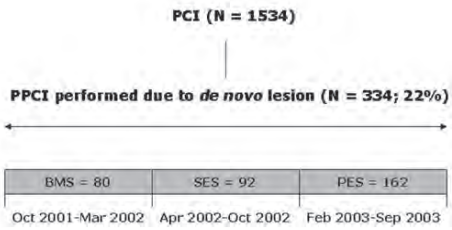

Figure 1. *The three cohorts in chronological order. All patients undergoing primary percutaneous coronary intervention (PPCI) were enrolled, including those with cardiogenic shock. Patients undergoing multiple revascularization procedures were only enrolled in the first original cohort and those receiving different stent types in the index procedure were excluded. BMS = bare-metal stent; SES = sirolimus-eluting stent; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent.*

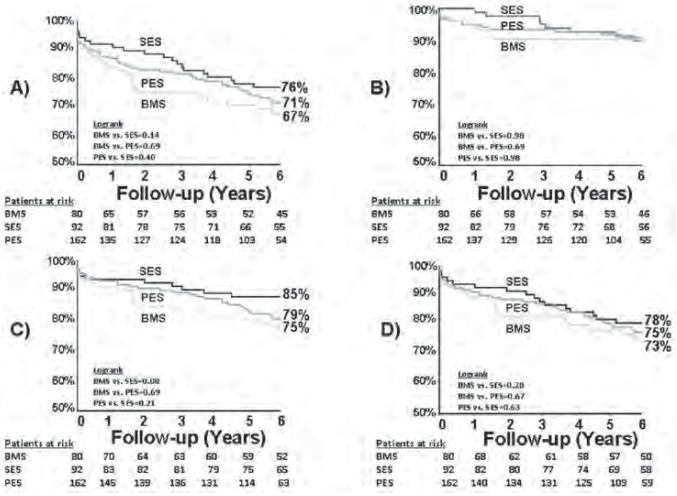

Figure 2. *Cumulative adverse cardiac event-free survival rates of ST-elevation myocardial infarction patients treated with bare-metal stents (BMS), sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES). (A) Major adverse cardiac event curve.(B) Target vessel revascularization (TVR) curve; TVR rates at 6 years: BMS = 91%; SES = 90%; PES = 91%. (C) Mortality curve. (D) Mortality/myocardial infarction curve.*

novo lesions in three "real world" registries in our academic hospital between October 2001 and September 2003 (Figure 1). Patients with a rescue PCI after failed thrombolysis, prior brachytherapy or receiving multiple stent types during the initial procedure were excluded from analysis. All other patients, including those with cardiogenic shock, remained in their first original enrolled cohort during the follow-up period.

The Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry was conducted from April 2002 until October 2002 and included 92 consecutive STEMI patients who were treated with only SES (*Cypher®, Cordis Corporation, Miami Lakes, Florida*). From February 2003 until September 2003, 162 consecutive STEMI patients were treated with the PES (*TAXUS™, Express2™ or Liberté™, Boston Scientific, Natick, Massachusetts*) as the default strategy for all PCI as part of the Taxus Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. These patients were compared with 80 BMS patients who were treated from October 2001 until March 2002.

All procedures were performed according to standard clinical guidelines and every patient was pre-treated with aspirin and ≥ 300 mg clopidogrel. The post-procedural dual-antiplatelet regimen consisted of ≥ 80 mg aspirin lifelong and ≥ 75 mg clopidogrel for at least 1 month if BMS were used, ≥ 3 months for patients with SES and ≥ 6 months for patients with PES. Periprocedural glycoprotein IIb/IIIa antagonists were used at the discretion of the treating interventional cardiologist. All of the repeat coronary angiographies were clinically driven by physical symptoms or diagnostic findings suggestive of myocardial ischemia.

Definitions and clinical endpoints. Definite stent thrombosis was defined as an angiographically documented thrombus in or within 5 mm of the stent, accompanied by at least one of the following criteria as recommended by the academic research consortium (ARC) criteria: 1) acute symptoms; 2) ischemic electrocardiographic changes; and 3) typical rise and fall of cardiac markers and categorized into early (within 30 days post-stent implantation), late (within 30 days and 1 year post-stent implantation) and very late (> 1 year post-stent implantation). The primary endpoint was the occurrence of MACE [defined as a composite of all-cause mortality, myocardial infarction (MI) and TVR]. Secondary efficacy endpoint included TVR, while safety endpoints consisted of all-cause mortality and the composite of all-cause mortality/MI. MI was diagnosed by recurrent typical clinical symptoms, the development of ST-segment elevation or left bundle branch block on electrocardiography with a CK-MB rise of 3 times the upper limit of normal and/or positive troponin levels in the laboratory values. TVR was defined as a repeat PCI in the same vessel as the index procedure, in the presence of ischemic symptoms or positive functional ischemia study on the target vessel area and a significant minimal luminal diameter stenosis of at least 50%.

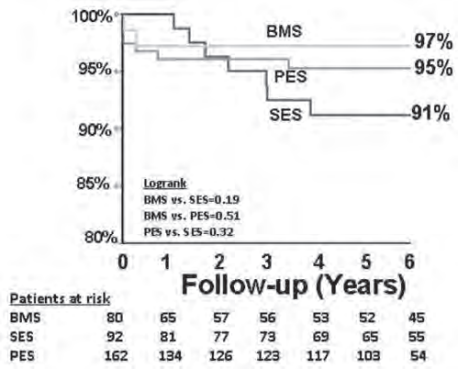

Figure 3. *Kaplan-Meier curves for stent thrombosis of the three stent types at 6-year follow-up. BMS = bare-metal stents; PES = paclitaxel-eluting stents; SES = sirolimus-eluting stents.*

Follow-up. The clinical status of treated PPCI patients was documented yearly by contacting municipal civil registries until December 2009. All living patients received a health-related questionnaire, consisting of queries regarding rehospitalization and cardiac events. The hospital records and coronary angiographies from our academic hospital or the referring institution were systematically reviewed in case of a patient-reported event.

Statistical analysis. Categorical baseline variables were tested with the Chi-square test and the ANOVA test was used for continuous baseline variables between the groups. The Kaplan-Meier method estimated the cumulative adverse cardiac events for the endpoints (all-cause mortality, all-cause mortality/MI, MACE and TVR) and the differences between the three stent curves were tested with the log-rank test.

Multivariate Cox proportional hazard regression model [95% confidence interval (CI) and p-value < 0.05 regarded as significant] was used to adjust for differences in baseline and procedural characteristics between the groups. All baseline variables with a $p \leq 0.5$ in univariable analysis were used in the multivariate Cox proportional hazard regression model. Stepwise backward deletion of the least significant variable was performed until all variables had a $p \leq 0.10$.

Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All statistical analyses were performed with SPSS for Windows version 17 (*SPSS Inc., Chicago, Illinois*).

Results

Population characteristics. Complete follow-up was available for 92.5% of patients. The clinical baseline and procedural characteristics of the three cohorts are shown in Table 1. Most of these characteristics were comparable between the three groups, except BMS patients were younger (p = 0.02), more often had a history of prior MI (p = 0.005) and were more likely to smoke cigarettes (p = 0.03) compared to SES and PES patients. The right coronary artery was more often the culprit (p = 0.02) and the diameter of the implanted stents was also larger in the BMS cohort (p < 0.001). Glycoprotein IIb/IIIa was more commonly prescribed to patients receiving BMS, and the clopidogrel intake was longer in both DES cohorts as mandated by the study protocol. The duration of clopidogrel usage post-stent implantation increased over time, being shortest for the BMS group (mean of 1 month) and the longest in the PES population (mean of 6 months).

6-year clinical outcome. Thirty-day, 1-year and 3-year clinical outcome have been reported previously.[15–17] The cumulative incidence and the associated adjusted hazard ratios (HR) (BMS versus SES, BMS versus PES, SES versus PES) of the 6-year follow-up of the STEMI-patients from the BMS cohort, RESEARCH and T-SEARCH are shown in Table 2 for each of the endpoints.

At 6 years, 21 (Kaplan-Meier estimate of 25%) of the BMS patients had died, compared to 14 (15%) of SES patients and 32 (21%) of PES patients, which was non-significant in univariate analysis. No significant differences were found for MACE and TVR rates between SES and PES (HR = 1.12, 95% CI: 0.86–1.44; HR = 0.99; 95% CI: 0.64–1.54, respectively). None of the endpoints were significantly different between the three stent types. Furthermore, MACE (HR = 0.77, 95% CI: 0.49–1.20), TVR (HR = 0.98, 95% CI: 0.42–2.31), mortality (HR = 0.72, 95% CI: 0.43–1.21) and mortality/MI (HR = 0.81, 95% CI: 0.50–1.32) rates did not decrease after bundling SES and PES into the broader DES group (n = 254 patients) compared to the BMS group.

The multivariate Cox regression analysis, which was used to correct for baseline differences and independent predictors of adverse events at 6 years, showed that all-cause mortality rates were lower in the SES group compared to the BMS group (aHR = 0.41, 95% CI: 0.17–0.98). Also, the all-cause mortality/MI and MACE rates were lower in the SES group. However, very late stent thrombosis was more common in SES patients compared to those receiving a PES or BMS (7.6% versus 0.6% versus 0%, respectively; p = 0.001) (Table 2). No significant differences were found on all endpoints between PES patients and BMS patients. The TVR rates of the three stent types were similar.

Discussion

This is the longest follow-up study comparing the safety and effectiveness of DES with BMS in a STEMI population in the real world. The usage of SES was still associated with a higher rate of very late stent thrombosis compared to PES and BMS at 6 years; however, no events were noted beyond 4 years of follow-up in the three cohorts. Noteworthy is the fact that the duration of clopidogrel use after DES implantation increased from 1 month to 1 year, which potentially effected the occurrence of late stent thrombosis of SES patients in our cohort.

After adjusting for differences in baseline and procedural characteristics, the rate of MACE was significantly lower in the SES patients when compared to BMS patients, driven primarily by a lower mortality rate at 6 years. No difference was observed in terms of TVR between the three stent types.

The benefits of DES over BMS use observed in patients with stable coronary artery disease population at 4 years were

Table 1. Baseline and procedural characteristics stratified according to stent type.

Number of patients	BMS	SES (n = 80)	PES (n = 92)	p-Value (n = 162)
Demographic characteristics				
Age (years)	55.7 ± 10	57.5 ± 11	59.8 ± 12	0.02
Male	77.5%	69.6%	82.7%	0.053
Cardiac history				
Prior MI	28.2%	15.2%	11.7%	0.005
Prior CABG	5.0%	1.9%	1.1%	0.2
Prior PCI	12.7%	6.5%	4.9%	0.1
Risk factors				
Current smoking	55.0%	51.1%	38.9%	0.03
Hypertension	28.8%	25.0%	25.3%	0.8
Hypercholesterolemia	36.3%	35.9%	36.4%	1.0
Diabetes	8.8%	13.0%	5.6%	0.1
Insulin-dependent	2.5%	3.3%	2.5%	0.9
Non-insulin dependent	6.3%	9.8%	3.1%	0.1
Family history	26.3%	34.8%	24.7%	0.2
Clinical presentation				
Cardiogenic shock	11.3%	13.0%	9.8%	0.7
Disease severity				
Multi-vessel disease	48.8%	39.1%	46.3%	0.4
Bifurcation	22.5%	30.4%	17.3%	0.3
Number of stents (n)	1.8 ± 0.9	1.9 ± 1.3	1.8 ± 1.1	0.5
Average stent diameter (mm)	3.3 ± 0.3	2.9 ± 0.1	3.1 ± 0.3	< 0.001
Total stent length (mm)	29.9 ± 18	33.6 ± 24	35.2 ± 23	0.2
Infarct-related coronary vessel				
RCA	22.5%	42.4%	37.7%	0.02
LAD	65.0%	42.4%	47.5%	0.008
LCX	11.3%	12.0%	11.1%	0.98
LM	1.3%	3.3%	2.5%	0.69
Bypass graft	0.0%	0.0%	1.2%	0.35
Thrombocyte aggregration inhibitor				
Clopidogrel duration (months)	2.0 ± 1.0	3.9 ± 2.1	6.0 ± 0.0	< 0.001
IIb/IIIa inhibitor	52.5%	35.9%	49.4%	< 0.001

Data are presented as percentages or means ± standard deviations.
BMS = bare-metal stent; SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent; MI = myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; RCA = right coronary artery; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; AHA = American Heart Association.

accrued in the first year after treatment.[18] After this period, there was no incremental benefit in terms of clinical events such that the early advantage was maintained in the long-term without significant catch-up. However, the incidence of very late stent thrombosis was higher in the DES groups. In the STEMI population, the use of DES is still controversial due to safety concerns, especially with the incidence of stent malapposition, delayed healing and subsequent stent thrombosis. The recent HORIZONS-AMI study has alleviated the concerns to some extent by demonstrating similar safety endpoints at 12 months in terms of death and stent thrombosis for both PES and BMS (3.5% and 3.5%, respectively; $p = 0.98$) and stent thrombosis (3.2% and 3.4%, respectively; $p = 0.77$).[19] This randomized trial with 3,006 patients presenting with STEMI confirmed earlier reports of superior efficacy with the DES. In fact, PES-treated patients had significantly lower 12-month rates of ischemia-driven target lesion revascularization (4.5% versus 7.5%; HR = 0.59; 95% CI: 0.43–0.83; $p = 0.002$). The 2-year outcomes of PES (n = 90) or SES (n = 90) versus BMS (n = 90) in the PASEO trial demonstrated retained benefit of DES in terms of TVR in a STEMI population.20 As with stable coronary artery disease, the advantage of DES over BMS had been accrued in the first year of follow-up already. On the other hand, in the MISSION! Intervention trial, the significant difference between SES (n = 158) and BMS (n = 152) patients for TVR at 1-year follow-up was no longer statistically significant at 3 years (TVR, 8.9% versus 15.8%; $p = 0.06$).21 Moreover, as observed in our current report, very late stent thrombosis was observed in the SES group as opposed to none in the BMS group, which may explain the catch-up in TVR rates seen on longer-term follow-up.

Thus, although the occurrence of stent thrombosis in our cohorts remained relatively low and non-different for both BMS and PES, a higher very late stent thrombosis rate in SES remains a realistic concern, and whether this is more common in patients treated for STEMI as compared to stable coronary artery disease remains to be demonstrated.

Similarly, the 3-year follow-up data of the SESAMI trial, which compared outcomes of 320 STEMI patients treated with BMS and SES, showed that the advantage of the latter in terms of target lesion revascularization (13.5% versus 7%; $p = 0.048$) was mainly accrued during the first year of follow-up, which coincided with the discontinuation of clopidogrel.[22] In the present study at 6 years, as well as in our previous report at

	BMS (n = 80)	SES (n = 92)	PES (n = 162)	BMS vs. SES	BMS vs. SES	PES vs. SES
	Number of events (%)			Multivariate HR (95% CI)		
MACE	28 (35.0%)	24 (26.1%)	46 (28.4%)	0.35 (0.17–0.72)	0.64 (0.37–1.08)	0.95 (0.73–1.23)
TVR	7 (8.8%)	10 (10.9%)	14 (8.6%)	0.84 (0.22–3.19)	0.91 (0.34–2.44)	1.03 (0.65–1.64)
Mortality	21 (26.3%)	14 (15.2%)	32 (19.8%)	0.41 (0.17–0.98)	0.67 (0.36–1.25)	0.84 (0.60–1.18)
Mortality/MI	23 (28.8%)	20 (21.7%)	38 (23.5%)	0.44 (0.21–0.96)	0.72 (0.40–1.30)	0.97 (0.73–1.28)
Early ST	1 (1.3%)	0 (0.0%)	4 (2.5%)	(overall p = 0.3)		
Acute ST	0 (0.0%)	0 (0.0%)	1 (0.6%)	(overall p = 0.6)		
Sub-acute ST	1 (1.3%)	0 (0.0%)	3 (1.9%)	(overall p = 0.4)		
Late ST	1 (1.3%)	0 (0.0%)	2 (1.2%)	(overall p = 0.6)		
Very late ST	0 (0.0%)	7 (7.6%)	1 (0.6%)	(overall p = 0.001)		
Total ST	2 (2.5%)	7 (7.6%)	7 (4.3%)	(overall p = 0.3)		

BMS = bare-metal stent; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; ST = stent thrombosis.
Early stent thrombosis is defined as stent thrombosis occurring within 30 days post-stent implantation, and is subcategorized into acute stent thrombosis (within 24 hours) and subacute stent thrombosis (1–30 days). Late stent thrombosis is defined as stent thrombosis occurring within 30 days and 1 year. Very late stent thrombosis is defined as stent thrombosis occurring after > 1 year after the index procedure.

4 years, we did not observe differences in the rates of TVR between DES and BMS. Although shorter-term follow-up of similar comparative studies in the STEMI population has found differences in this endpoint at 1 year, our findings may reflect a failure of sustained DES superiority in the longer term. However, the lack of statistical difference was also reported in the pROSIT trial, which compared SES to PES in PPCI patients.[23] This trial showed comparable clinical outcomes of both stents at 1 year.[23] The study, which included 6-month angiographic follow-up, failed to show statistical superiority of SES despite lower late loss and numerically higher rates of binary stenosis. However, both this and our study results have to be considered with caution. First, the DES group in our RESEARCH and T-SEARCH registries had longer stented segments, as opposed to longer stents in the BMS group in more contemporary randomized trials.[24] Second, the study is underpowered to definitely conclude equality in safety and efficacy of these stents in MI. Interestingly, SES-treated patients showed a survival advantage in our cohort. Although no major trial suggested a lower mortality rate with DES when compared with BMS, an observational study by Mauri et al reported a lower risk-adjusted mortality rate for patients treated with DES for MI (10.7% versus 12.8%; $p = 0.02$).25 The superiority of SES over BMS in our cohort was attributed to a lower mortality in the DES group, whereas TVR was not different. Restenosis has been shown to be associated with increased risk of death and MI.[26] Since our patients are real-world registry patients with no regular angiographic follow-up, in the long term, mortality may be one of the manifestations of undetected/inadequately treated myocardial ischemia secondary to subclinical restenosis.

The current analysis has some limitations worthy of note. First, it is observational in nature and differences in baseline clinical variables and adjunctive treatment during the specific time periods may have resulted in revascularization and/or mortality rate advantage. Although statistical adjustment for confounders was performed, this may still have been inadequate, especially given the small number of patients in the three stent groups. Second, some events could have been missed due to the fact that only living patients are asked to self-report events.

In conclusion, very late stent thrombosis is still an issue of concern at 6-year follow-up for first-generation SES. This did not jeopardize the survival advantage or rate of MACE in the SES group when compared to BMS. No differences were found in the TVR rates of between the three stent types. These findings need to be addressed in the long-term follow-up of the randomized trials.

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5.6 Value of the SYNTAX Score in Patients Treated by Primary Percutaneous Coronary Intervention for Acute ST Elevation Myocardial Infarction - the MI SYNTAXscore Study.

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Value of the SYNTAX score in patients treated by primary percutaneous coronary intervention for acute ST-elevation myocardial infarction: The MI SYNTAXscore study

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Aims The aims of this study were to evaluate the SYNTAX score (SXscore) calculated at 2 stages during a primary percutaneous intervention (PPCI), that is, SXscore I (diagnostic) and SXscore II (postwiring), and assess its additional value to standard clinical risk scores in acute myocardial infarction.

Methods and Results SXscores I and II were applied to 736 consecutive acute ST-elevation myocardial infarction patients referred for PPCI between November 2006 and February 2008. SXscore changed significantly before (I: 16, interquartile range 9.5-23) and after wiring (II: 11, interquartile range 6-19), $P < .001$. Kaplan-Meier methods were used to compare the primary end point major adverse coronary events (MACE; composite of repeat MI, target vessel revascularization [TVR], and mortality) and secondary end point mortality at 1.5 years in tertiles of SXscore I and SXscore II. Major adverse coronary event was highest in the higher SXscore I tertile (11% vs 15% vs 23%, log-rank <0.01), driven primarily by increased rate of mortality (9% vs 11% vs 17%, log-rank 0.02). Major adverse coronary event was also highest in SXscore II tertile, by a combination of increased mortality and also TVR (TVR rate 2% vs 3% vs 9%, log-rank <0.01). Predictive Cox regression models for mortality and MACE were significantly and similarly improved by the addition of either SXscore I or SXscore II (hazard ratio 1.63, 95% CI 1.18-2.26, $P < .01$ for MACE) with respective *c* indices of 0.61 and 0.63 for MACE and 0.60 and 0.61 for mortality.

Conclusions SXscore during PPCI is a useful tool that provides additional risk stratification to known risk factors of long-term mortality and MACE in patients with ST-elevation myocardial infarction. (Am Heart J 2011;161:771-81.)

The SYNTAX score (SXscore)[1] is a tool that can be used to cumulatively quantify the extent of angiographic coronary artery disease. It has been developed from the Leaman score[2] and therefore takes into account not only the number of lesions, their location, and characteristics but also their functional impact. In fact, scoring of lesions is weighed according to the size of the perfused territory of the left ventricle. The SXscore has been shown to be a good predictor of adverse cardiovascular events including cardiac death, myocardial infarction (MI), and target lesion revascularization in patients treated with percutaneous coronary intervention (PCI) for complex disease.[3-4]

Coronary angiographic characteristics at primary percutaneous intervention (PPCI) that are known to affect prognosis include culprit artery (left vs right), thrombolysis in MI (TIMI) flow at presentation, and the presence of multivessel disease especially chronic total occlusions (CTOs).[5-7] The SXscore derived from the diagnostic phase of the PPCI can quantify these features. By consideration of whether the culprit lesion is occluded on presentation and accordingly scoring it as a total occlusion or otherwise, it can incorporate a numerical value that takes into account both the volume and degree of ischemic left sided myocardium. The SXscore derived after wiring of the culprit lesion defines better the underlying culprit vessel anatomy in cases where this is obscured by the occlusion in the diagnostic phase.

The detailed anatomical and functional consideration of the SXscore may make it an attractive quantification tool for

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use as a prognostic indicator in patients presenting with ST-elevation MI (STEMI). To this end, we set out to investigate the predictive value of the SXscore on long-term outcomes in patients undergoing PPCI. The aims of our study are 2-fold. First, we calculated the SXscore derived at the 2 stages during a PPCI procedure and assessed their predictive value for long-term clinical outcome. Second, we studied whether the SXscore is able to offer additional predictive value of long-term clinical outcome when compared with the classical risk factors for survival and major adverse coronary events (MACEs) in STEMI.

Methods

Between November 2006 and February 2008, 736 consecutive patients undergoing primary PCI for STEMI in our institution were screened for inclusion in the MI SYNTAXscore study. All patients in the referral area of the Thoraxcentre, Erasmus MC, Rotterdam, who had symptoms of acute MI (<12 duration) were assessed clinically and by 12-lead electrocardiogram by paramedical personnel or peripheral hospital medical staff. Those who met the criteria of acute MI were transported immediately to our center for PPCI. Pretreatment with aspirin, clopidogrel, and heparin was administered prehospital. Urgent diagnostic angiography was followed by PPCI if appropriate. The procedure was performed using standard techniques. Drug-eluting stents were implanted as first-line choice of stents. Treatment of complications such as cardiogenic shock and cardiac arrest was performed according to guidelines.

Baseline clinical characteristics and procedural characteristics were prospectively recorded in a dedicated electronic database. For the purpose of this study, the only exclusion criteria were patients with previous coronary artery bypass grafting (CABG) in whom the SXscore could not be calculated. The SXscore for each patient was calculated by a team of 2 interventional cardiologists. All coronary lesions with a diameter stenosis ≥50% in vessels ≥1.5 mm were scored using the SXscore algorithm, which is available on the Web site (www.syntaxscore.com). In case of disagreement with regard to the significance of a lesion, quantitative coronary angiography was applied and the lesion included if it was ≥50%. On agreement between the 2 cardiologists, the data were entered onto a dedicated software program. SYNTAX scoring was performed at 2 predefined stages of the index procedures:

SXscore I: initial diagnostic angiogram. This takes into account the patency of the infarct-related artery (IRA). Thus, an IRA with a TIMI flow of 0 or 1 is scored as a total occlusion with thrombus.

SXscore II: after wiring/small balloon. If TIMI flow improves with these measures, this allows assessment of lesion severity as well as additional disease downstream. On the other hand, persistence of a TIMI 0/1 that does not allow adequate visualization of the lesion is scored as in SXscore I (total occlusion with thrombus).

The investigators calculating the SXscore were blinded to the patients' clinical characteristics. The scoring was done prospectively at each stage so that the investigators were blinded to the next stage film, to the procedural data, and to the clinical outcomes. No change in scoring was allowed once a score was assigned.

Intraobserver and interobserver variability

The first 100 consecutive films from the cohort were analyzed by a third independent observer to obtain interobserver variability and by the same team 8 weeks after the first scoring phase to obtain intraobserver variability. The investigators remained blinded to the results of the first analysis. This number of patients was selected based on our previous experience with the variability of the SXscore.[8]

Follow-up

Survival data for all patients were obtained from the municipal registry. A health questionnaire was subsequently sent to all living patients with specific questions on readmission and MACE. For patients with an adverse event at another center, medical records, discharge summaries, and, when necessary, angiographic films were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. Events were adjudicated by 2 experienced interventional cardiologists according to the definitions below. Written informed consent was obtained from all patients.

Definitions

ST-elevation MI was diagnosed when patients had symptoms of an acute MI lasting at least 30 minutes and accompanied by >1 mm (0.1 mV) ST elevation in 2 or more contiguous leads and later confirmed by a cytokeratin (CK) and CK-MB rise and /or troponin rise.

Thrombolysis in MI flow grade and corrected TIMI frame count as well as myocardial blush grade (MBG) at the start and end of the procedure were determined from the angiographic films as previously described.[9,10] Target lesion revascularisation (TLR) was defined as any PCI of the index lesion and including the 5-mm adjacent segments in either main vessel or side branch. Stent thrombosis was defined according to the Academic Research Consortium.[11]

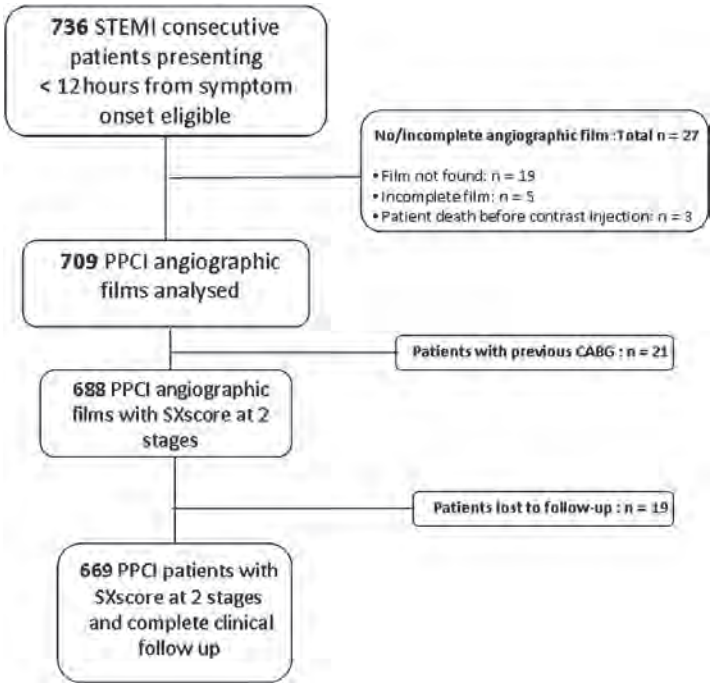
Primary and secondary end points

The primary clinical end point was MACE at 1.5 years, defined as a composite of cardiac or noncardiac death, repeat MI, and ischemia-driven target vessel revascularization (TVR). Repeat MI in the acute post-PPCI phase was defined as clinical signs of reinfarction with recurrent or persistent symptoms and ST-segment changes and requiring a repeat PPCI and/or a second peak in the CK-MB mass or troponin-T/troponin-I increase to ≥3 times the upper limit of normal not related to an interventional procedure and new pathological Q waves in 2 or more contiguous electrocardiograph leads. A repeat MI postdischarge was defined as in the definitions section above. Target vessel revascularization was defined as revascularization of any part of the index coronary artery. Secondary end points included separately, all-cause mortality, repeat MI, and TVR.

Statistical analysis

Normality assumption for continuous variables was evaluated by the Kolmogorov-Smirnov test. These are presented as

Figure 1



Flow chart of the MI SXscore study population.

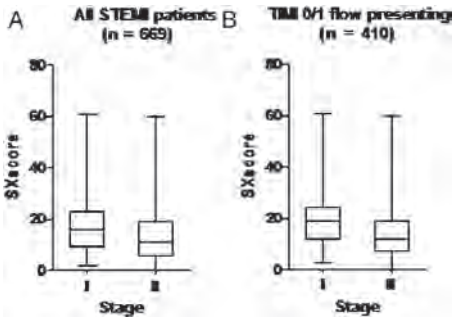
mean ± 1 SD or as median and interquartile range accordingly. Student unpaired *t* test or Mann-Whitney nonparametric tests were used to evaluate differences in continuous variables. Categorical variables are presented as counts and percentages, and differences in categorical variables between subgroups were evaluated with χ^2 test or Fisher exact test. The cohort was divided into 3 groups determined by SXscore tertiles. Levene's homogeneity-of-variance test was used to test for equal variance. For those variables meeting the assumption of equal variance, analysis of variance (ANOVA) was used to describe differences between the 3 groups. If the ANOVA assumptions were not met, we used the Kruskal-Wallis one-way ANOVA.

Kaplan-Meier method was used to generate cumulative survival curves and curves of event-free survival for the various predefined end points, and the log-rank test was used to assess the difference in survival between SXscore tertile groups. Independent variables from multivariable analysis were used to assess the significance of SXscore I and SXscore II and its contribution to improvement of the model with respect to the primary and secondary end points as measured by *c* indices. To explore the applicability of the findings in our cohort to other STEMI populations, we also assessed the addition of the scores to the widely used TIMI risk score with variables including age, diabetes, hypertension, systolic blood pressure, heart rate, Killip class, weight, and anterior STEMI. On multivariate analysis, we determined whether adding SXscore improved the model significantly. The omnibus test of model coefficients was used to assess the improvement of the model. Proportionality of hazards was tested graphically based on visual inspection of log-log survival curves and by performing a formal test of proportionality based on Schoenfeld residuals for each variable in the model.[12] The performance of the multivariate model with the SXscore was studied with respect to calibration. Calibration refers to whether the model agrees with the observed probabilities; it was measured with the Hosmer-Lemeshow goodness-of-fit test.

The weighted κ value determined the intraobserver and interobserver variability. A κ value of >0.0 to ≤0.2 was considered slight; >0.2 to ≤0.4, fair; >0.4 to ≤0.6, moderate; >0.6 to ≤0.8, substantial; and >0.8 to ≤1.0, almost perfect.[8]

All statistical tests were 2-tailed, and *P* values were significant at <.05. Analysis was performed using SPSS software version 17.0 (SPSS, Chicago, IL).

Figure 2



Box plots showing the SXscore at the 2 stages during PPCI; SXscore I obtained from the diagnostic stage and SXscore II obtained after wiring or after use of a small balloon. **A**, The SXscore changed significantly from I to II when tested with Kruskal-Wallis and subsequently Mann-Whitney tests. **B**, When patients with TIMI 0/1 only are considered, higher change from I (median 19) to II (median 12) is observed.

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting, and editing of the paper and its final contents.

Results

From the initial 736 patients screened, 27 were excluded due to unavailability of a complete diagnostic coronary angiogram, whereas 21 were excluded because they had prior CABG. Survival status and follow-up could not be obtained in 19 patients. Thus, the final number of patients included in our analysis was 669 as shown in Figure 1.

Among the 669 patients, 385 (58%) had significant disease in at least 1 vessel other than the IRA. The median SXscore I was 16 (interquartile range [IQR] 9.5-23). Thrombolysis in MI 0/1 flow in the IRA was present in 61% of patients. The median SXscore II was 11 (IQR 6-19). Stent implantation was deemed appropriate and performed in 616 (92%) of patients.

There were significant differences between SXscores I and II, $P < .001$ as determined by the Kruskal-Wallis test. This is illustrated in Figure 2. The difference between the stages were more apparent on analysis of TIMI 1/0 presenting subgroup (Figure 2B) I (19, IQR, 12-24.5) versus II (12, IQR: 7-19), $P < .001$.

The differences in basal clinical characteristics, angiographic characteristics, procedural characteristics, and follow-up management according to 3 tertiles of SXscore I are shown in Tables I and II. Patients with higher SXscore I were older and more commonly had previous MI. These patients also presented with higher pulse rates, cardiogenic shock, and anterior STEMI. The left anterior descending artery (LAD) was more commonly the culprit in the higher tertile, whereas the right coronary artery (RCA) was more commonly the IRA in the lowest tertile. Stents implanted in the patients with higher scores were longer and more likely to involve bifurcations. Procedure failure with TIMI 0/1 flow, low MBG, and high corrected TIMI frame count (cTFC) were more common in the highest tertile. Complete revascularization within 3 months was more commonly achieved in patients with lower scores.

Similarly, for Sxscore II (Tables III and IV), significantly higher scores were observed in patients with a previous MI and those presenting with cardiogenic shock. Patients with higher scores were more likely to have longer stents implanted, more bifurcation treatment, and multivessel stenting during the index procedure. Procedure failure with final TIMI flow 0/1 and impaired myocardial perfusion

Table I. Clinical characteristics of patients presenting with MI according to SXscore I tertiles

	SXscore I tertiles			
	Lower (<10), n = 209	**Intermediate (10-20), n = 241**	**Higher (>20), n = 219**	***P****
Baseline characteristics				
Age (y)	63 ± 13	64 ± 13	68 ± 11	<.01
Male	135 (64)	171 (71)	163 (74)	.08
Diabetes	14 (8)	21 (9)	28 (13)	.09
Type 1	9 (4)	7 (3)	12 (6)	.39
Type 2	5 (2)	15 (6)	17 (8)	.04
Hypertension	61 (29)	87 (36)	76 (35)	.27
Hypercholesterolemia	40 (19)	51 (21)	49 (22)	.71
Smoker				
Current	100 (48)	105 (44)	75 (34)	.01
Former	31 (15)	29 (12)	31 (14)	.66
Renal failure	3 (1)	7 (3)	8 (4)	.35
Family history of CAD	79 (38)	73 (30)	58 (27)	.04
Body mass index (kg/m^2)	27 ± 4	27 ± 4	27 ± 4	.74
Previous MI	12 (6)	33 (14)	40 (18)	<.01
Previous PCI	19 (9)	23 (10)	22 (10)	.95
Clinical presentation				
Symptom onset to balloon time >90 min	168 (87)	179 (83)	174 (87)	.38
Out-of-hospital cardiac arrest	8 (4)	10 (4)	13 (6)	.53
Pulse rate (beat/min)	78 ± 17	77 ± 17	81 ± 18	.04
Blood pressure (mm Hg)				
Systolic	123 ± 26	126 ± 27	122 ± 27	.29
Diastolic	75 ± 13	76 ± 15	74 ± 17	.45
Cardiogenic shock	11 (5)	15 (6)	29 (13)	<.01
Killip classes 2-4	11 (5)	19 (8)	22 (10)	.18

Data are expressed in numbers (percentages) and mean ± 1 SD. Percentages are rounded.
*P value calculated using ANOVA for continuous variables or Kruskal-Wallis test for nonparametric variables and χ^2 test for categorical variables.

Table II. Angiographic characteristics, procedural characteristics, and management of patients with acute MI according to SXscore I tertiles

	SXscore I tertiles			
	Lower (<10), n = 209	**Intermediate (10-20), n = 241**	**Higher (>20), n = 219**	***P****
Angiographic characteristics preprocedural				
Anterior STEMI	70 (34)	128 (53)	106 (48)	<.01
IRA				
Left main	0 (0)	1 (0.4)	4 (2)	.12
Left anterior descending	63 (30)	115 (48)	102 (47)	<.01
Left circumflex	39 (19)	42 (17)	28 (13)	.21
Right coronary	106 (51)	83 (34)	86 (39)	<.01
TIMI 0/1 in IRA	73 (35)	169 (71)	168 (77)	<.01
Stent thrombosis (cause)	4 (2)	13 (5)	8 (4)	.15
Diseased vessels including IRA				
1-vessel disease	158 (76)	95 (39)	28 (13)	<.01
2-vessel disease	40 (19)	103 (43)	63 (29)	<.01
3-vessel disease†	10 (5)	43 (18)	128 (58)	<.01
Left main disease	4 (2)	3 (1)	35 (16)	<.01
CTO	2 (1)	3 (1)	41 (19)	<.01
Procedural characteristics				
Stent implantation	196 (94)	225 (93)	195 (89)	.10
Total stent length (mm)	26 (18-36)	28 (23-46)	32 (23-51)	<.01
Stent diameter (mm)	3.3 ± 0.5	3.1 ± 0.5	3.2 ± 0.5	.02
Bifurcation treatment in IRA	20 (10)	55 (23)	48 (22)	<.01
Thrombectomy	37 (18)	45 (19)	42 (19)	.92
GP IIb/IIIa inhibitors	46 (22)	52 (22)	49 (22)	.98
Inotropic agents	10 (5)	9 (4)	12 (6)	.67
Intra-aortic balloon pump	8 (4)	13 (5)	24 (11)	.01
Multivessel stenting	15 (7)	26 (11)	28 (13)	.16
Angiographic characteristics postprocedural				
TIMI 0/1	3 (1)	7 (3)	18 (8)	<.01
Corrected TIMI frame count at end procedure (fps)	24 (16-36)	24 (18-35)	28 (20-44)	.05‡
Myocardial blush grade 0/1	1 (1)	5 (2)	16 (7)	<.01
Follow-up treatment				
Complete revascularization within 3 mo (PCI n = 331, CABG n = 4)	180 (86)	119 (49)	36 (16)	<.01
Medication at 1 y				
Aspirin	182 (87)	200 (83)	191 (87)	.60
Clopidogrel	203 (97)	231 (96)	203 (93)	.13
β-Blocker	192 (92)	209 (87)	188 (86)	.41
ACE inhibitors	117 (56)	157 (65)	166 (69)	.20
Statins	178 (86)	219 (91)	204 (93)	.45

Data are expressed in numbers (percentages), mean ± 1 SD, or median and (interquartile range). Percentages are rounded. *GP*, glycoprotein. *ACE*, angiotensin-converting enzyme.
* *P* value calculated using ANOVA for continuous variables and χ^2 test for categorical variables.
† Includes cases with left main disease plus 1-vessel disease.
‡ *P* value by Kruskal-Wallis test.

as determined by MBG was more common in the tertiles with the higher scores. Whereas complete revascularization within 3 months was achieved in 88% of patients in the lower tertiles, that in the highest tertile was low at 12.6%.

Long-term clinical outcome

All patients were followed up to 1.5 years. Mortality rate was 12.1%; TVR, 4.6; MI, 2.2%; and cumulative MACE, 16.4%. Angiographically defined stent thrombosis occurred in 1.2%. Kaplan-Meier curves for survival, repeat MI, and TVR, according to the tertiles of SXscore I, are shown in Figure 3. Log-rank test shows that the differences in mortality were significant between the highest and lower 2 tertiles. There were no statistically significant differences between tertiles for repeat MI and TVR so that the difference in MACE between tertiles was primarily driven by difference in mortality. Stent thrombosis, although numerically higher in the highest tertile, was not statistically different (1% vs 0.4% vs 2.3%, log-rank 0.17) Figure 4 shows the Kaplan-Meier curves for SXscore II. Log-rank test shows difference in mortality (9% vs 11% vs 17%, log-rank 0.02) and TVR (2% vs 3% vs 9%, log-rank <0.01) between the higher and lower tertiles but not between the intermediate and lower tertiles. There was no difference in repeat MI. The difference in MACE

Table III. Clinical characteristics of patients presenting with MI according to SXscore II tertiles

	Lower (<9), n = 238	Intermediate (9-17), n = 208	Higher (>17), n = 223	P*
Baseline characteristics				
Age (y)	62 ± 12	66 ± 13	68 ± 11	.10
Male	157 (66)	145 (70)	167 (75)	.10
Diabetes				
Type 1	9 (4)	5 (2)	14 (6)	.12
Type 2	8 (3)	10 (5)	19 (9)	.46
Hypertension	74 (31)	70 (34)	80 (36)	.55
Hypercholesterolemia	51 (21)	36 (17)	53 (24)	.25
Smoker				
Current	117 (52)	90 (44)	73 (35)	<.01
Former	31 (13)	27 (13)	33 (16)	.82
Renal failure	3 (1)	5 (2)	10 (5)	.10
Family history of CAD	93 (39)	63 (30)	54 (24)	<.01
Body mass index (kg/m^2)	27 ± 4	27 ± 4	27 ± 4	.51
Previous MI	14 (6)	27 (13)	44 (20)	<.01
Previous PCI	24 (10)	19 (9)	21 (9)	.94
Clinical presentation				
Symptom onset to balloon time >90 min	189 (86)	161 (85)	171 (86)	.98
Out-of-hospital cardiac arrest	8 (3)	7 (3)	16 (7)	.09
Pulse rate (beat/min)	77 ± 17	78 ± 17	81 ± 19	.09
Blood pressure (mm Hg)				
Systolic	126 ± 26	122 ± 27	122 ± 27	.87
Diastolic	76 ± 13	74 ± 17	74 ± 15	.25
Cardiogenic shock	13 (6)	14 (7)	28 (13)	.01
Killip classes 2-4	11 (5)	14 (7)	27 (12)	.01

Data are expressed in numbers (percentages) and mean ± 1 SD. Percentages are rounded.
* *P* value calculated using ANOVA for continuous variables or Kruskal-Wallis test for nonparametric variables and χ^2 test for categorical variables.

between the highest and lower tertiles is determined mostly by differences in mortality, followed by TVR. Angiographic stent thrombosis was higher in the highest tertile (0.8% vs 1% vs 1.8%, log-rank 0.60).

A Cox regression model with independent variables from our data was significantly improved in discrimination for both mortality and MACE when SXscore I or Sxscore II was added to the model. The *c* indices for SXscore I were 0.60 and 0.61 for mortality and MACE, respectively, whereas the *c* indices for SXscore II were 0.61 and 0.63 for mortality and MACE, respectively. Similarly, when only TIMI risk score variables for STEMI were introduced in the model, SXscore showed a significant improvement. (Table V). In fact, adding either SXscore I or Sxscore II to the TIMI risk score model improved the prediction of MACE ($P \leq .01$) and mortality ($P \leq .04$). Hazards ratio for mortality with a 20-point increase in the SXscore in a combined model adjusted for TIMI risk variables was 1.52 (1.03-2.23, $P = .04$) and 1.51 (1.03-2.21, $P = .03$) for SXscores I and II, respectively. For MACE, hazards were 1.63 (1.17-2.27, $P < .01$) for SXscore I and 1.63 (1.18-2.26, $P < .01$) for SXscore II, respectively.

Interobserver and intraobserver variability

Interobserver variability as measured by the weighted κ statistic was moderate (0.56 for both SXscores I and II). Intraobserver variability was substantial with values of 0.70 and 0.77 SXscores I and II, respectively.

Discussion

The SXscore, originally designed for quantifying stable coronary artery disease, can be usefully utilized in a STEMI population with disease in the native coronary arteries as demonstrated in our study. The extent of coronary artery disease and the successful intervention as determined by angiography at each stage during a PPCI and as graded by SXscores I and II are associated with the rate of mortality and MACEs both at 1.5-year follow-up. Both SXscores are independent predictors of mortality and MACE adding incremental value to the TIMI risk score in STEMI patients treated with PPCI. This therefore adds to the well-established risk factors of mortality as previously described in the major trials that studied the STEMI population.[13-15] In addition, the score can be used by clinicians, interventional cardiologists, and cardiac surgeons to better assess and quantify the risk of complications and tailor management strategies accordingly. This is the first study that reports the prognostic value of the SXscore, calculated purposely and exclusively for STEMI patients at 2 stages with the methodology described. Moreover, since more than 99% of our cohort were treated with drug-eluting stents in the setting of MI, the study results are the first to show applicability of the SXscore in a "real world" population with STEMI, treated almost exclusively with drug-eluting stents.

Risk scores in STEMI

The predictive power of clinical parameters derived from independent risk factors from the major reperfusion in acute coronary syndrome studies including the TIMI trials, Global Registry of Acute Coronary Events (GRACE), and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) is considerable.[14,15] Angiographic characteristics that have additional independent prognostic significance include the IRA, patency of the IRA, presence of 3-vessel disease, and CTOs. This present study highlights the importance of more detailed characterization of coronary artery disease in patients undergoing PPCI. In this present era of treatment of IRA lesions with stent implantation whenever possible, information about the lesion complexity is useful for the prediction of future events, which include revascularization of the target vessel, stent thrombosis, and repeat MI in the territory of the index IRA. In fact, 1.5-year TVR rates are considerably higher in patients in the higher SXscore II tertile. The higher disease complexity, the lower PCI success rate, as well as the need for longer, more overlapping stents and bifurcation treatment are

Table IV. Angiographic characteristics, procedural characteristics, and management of patients with acute MI according to SXscore II tertiles

	SXscore II tertiles			
	Lower (<9), n = 238	**Intermediate (9-17), n = 208**	**Higher (>17), n = 223**	***P****
Angiographic characteristics preprocedural				
Anterior STEMI	85 (36)	119 (57)	100 (45)	<.01
IRA				
Left Main	2 (1)	0 (0)	3 (1.3)	.26
Left anterior descending	75 (32)	111 (53)	94 (42)	<.01
Left circumflex	45 (19)	27 (13)	37 (17)	.23
Right coronary	116 (48)	70 (34)	89 (40)	<.01
TIMI 0/1 in IRA	136 (57)	130 (63)	144 (65)	.26
Stent thrombosis (cause)	5 (2)	13 (6)	7 (3)	.06
Diseased vessels including IRA				
1-vessel disease	189 (79)	76 (37)	16 (4)	<.01
2-vessel disease	42 (18)	96 (46)	68 (31)	<.01
3-vessel disease†	6 (3)	36 (17)	139 (62)	<.01
Left main disease	5 (2)	1 (1)	36 (16)	<.01
CTO	3 (1)	3 (1)	40 (18)	<.01
Procedural characteristics				
Stent implantation	218 (92)	198 (95)	200 (90)	.10
Total stent length (mm)	24 (18-32)	28 (23-51)	32 (23-51)	<.01
Stent diameter (mm)	3.3 ± 0.5	3.2 ± 0.5	3.3 ± 0.5	.09
Bifurcation treatment in IRA	17 (7)	47 (23)	59 (27)	<.01
Thrombectomy	52 (22)	37 (18)	35 (16)	.22
GP IIb/IIIa inhibitors	56 (24)	46 (22)	45 (20)	.69
Inotropic agents	8 (3)	8 (4)	15 (5)	.19
Intra-aortic balloon pump	9 (4)	11 (5)	25 (11)	<.01
Multivessel stenting	11 (5)	25 (12)	33 (15)	<.01
Angiographic characteristics postprocedural				
TIMI 0/1	3 (1)	6 (3)	19 (9)	<.01
Corrected TIMI frame count at end procedure (fps)	26 (18-32)	32 (21-36)	28 (20-33)	.02‡
Myocardial blush grade 0/1	1 (1)	5 (2)	16 (7)	<.01
Follow-up treatment				
Complete revascularization within 3 mo (PCI n = 331, CABG n = 4)	210 (88)	97 (47)	28 (13)	<.01
Medication at 1 y				
Aspirin	200 (84)	177 (85)	198 (89)	.60
Clopidogrel	228 (96)	202 (97)	205 (92)	.03
β-Blocker	212 (89)	185 (89)	194 (87)	.85
ACE inhibitors	150 (63)	123 (59)	154 (69)	.44
Statins	207 (87)	183 (88)	210 (94)	.33

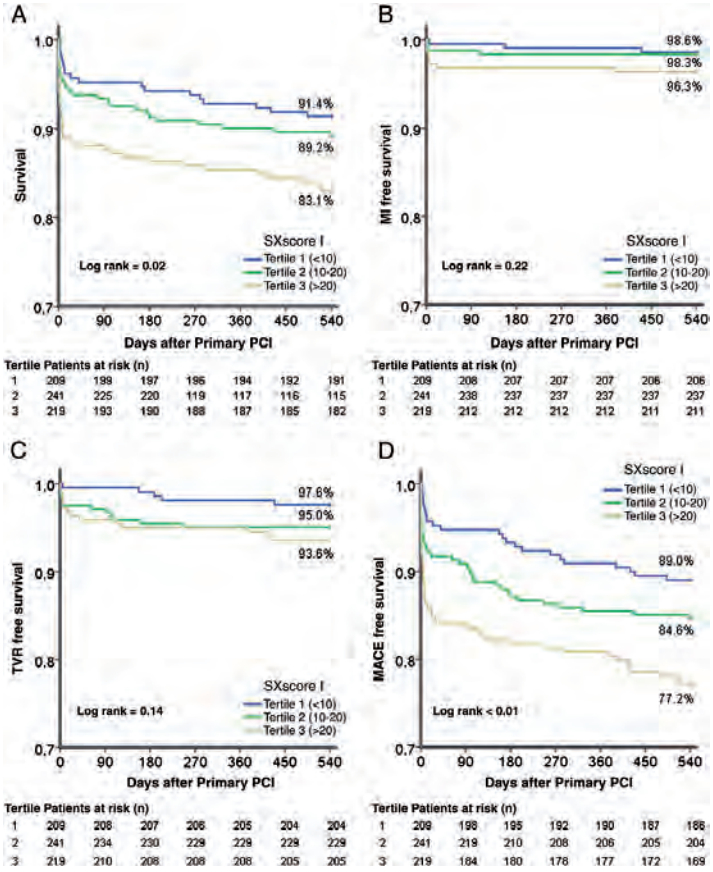
Data are expressed in numbers (percentages), mean ± 1 SD, or median and (interquartile range). Percentages are rounded. *GP*, glycoprotein; *ACE*, angiotensin-converting enzyme.
* *P* value calculated using ANOVA for continuous variables and χ^2 test for categorical variables.
† Includes cases with left main disease plus 1-vessel disease.
‡ *P* value by Kruskal-Wallis test.

likely contributing factors for the increased need of revascularization in this patient subgroup.

Functional consideration of the SXscore

By consideration of the flow to the left ventricle at the site of the lesion, a functional aspect has been added to the score. Thus, for a right-dominant coronary artery system, the RCA supplies approximately 16% of the flow to the left ventricle, whereas the left coronary artery supplies 84%. In a left-dominant system, the LAD supplies 66% and the left circumflex artery supplies 33% of the flow to the left ventricle. Appropriately, the SXscore assigns 1 to the RCA lesions, 1.5 to the left circumflex artery (LCx), and 3.5 to the LAD in consideration of function alone. In STEMI, a larger left ventricular infarct size can be anticipated when the culprit lesion is in the LAD. The level at which the occlusion occurs is also given weight in the score so that more proximal lesions, which supply a larger myocardial territory, carry higher scores. Moreover, SXscore I assigns a higher value to IRAs, which have TIMI 1/0 flow on diagnostic angiography during PPCI. Thus, further points are added and may be appropriate because the extent of myocardial damage is known to be higher in patients presenting with closed versus patent IRAs. This functional combination is a plausible reason for the better early separation of the survival curves between all 3 tertiles of SXscore I when

Figure 3



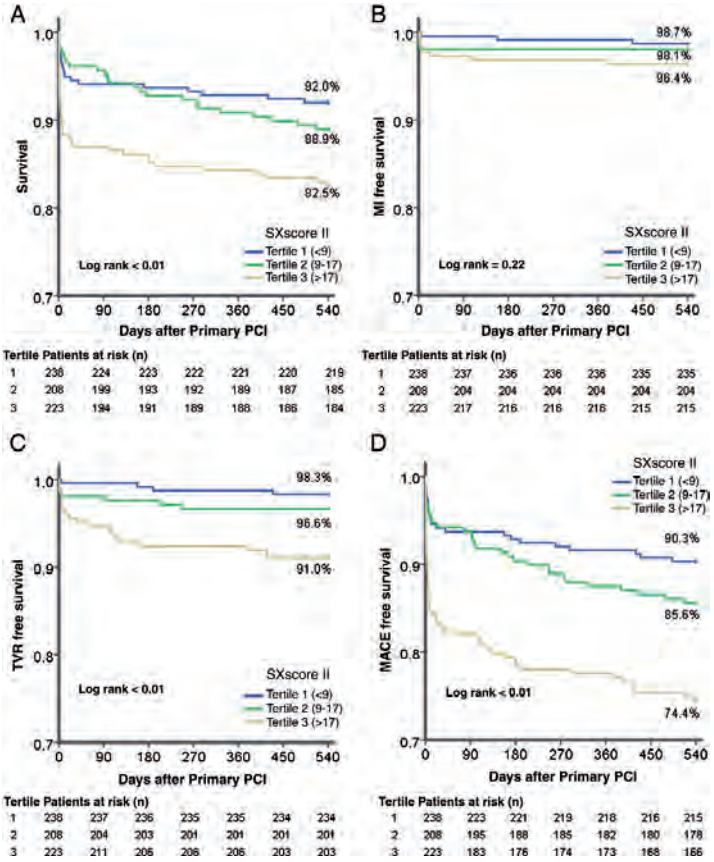
Kaplan-Meier event-free survival curves and their log-rank tests for patients presenting with STEMI and categorized in tertiles of the SXscore I. **A**, 1.5-year mortality. **B**, Repeat MI. **C**, TVR. **D**, MACE.

compared with SXscore II as illustrated in Figures 3 and 4, respectively.

Lesion complexity consideration

Angiographic characterization of the culprit lesion is possible in most patients presenting with acute STEMI. Patients with a patent IRA with TIMI 2 or higher flow can have characterization outright from the diagnostic angiography, unless the thrombus burden is high. In patients presenting with an occluded IRA with TIMI 1/0 flow, wiring or use of a small balloon can increase the flow to reveal the underlying lesion anatomy. SXscore II in these patients is lower than SXscore I because the increase in flow reduces the 5 points added in the latter for total occlusion. Patients in whom TIMI 0/1 flow persists after wiring may have higher intracoronary pressures from larger infarct sizes and possibly higher thrombus burden, which is associated with a poorer prognosis.[16] In addition, higher SXscores are assigned to patients with complex lesions with points added for trifurcations, bifurcations, ostial stenosis, severe tortuosity, lesion length >20 mm, heavy calcification, thrombus, and diffuse disease or small

Figure 4



Kaplan-Meier event-free survival curves and their log-rank tests for patients presenting with STEMI and categorized in tertiles of the SXscore II. **A**, 1.5-year mortality. **B**, Repeat MI. **C**, TVR. **D**, MACE.

vessels.[1] Although these features are historically and, in our study, more prevalent in patients who already have a poorer prognosis based on their high clinical risk factors alone (age, diabetes, smokers), SXscore can still give additional prognostic information. The better characterization of the underlying disease anatomy in the SXscore II may be a major reason for the better prognostic impact on MACE in the long term.

Multivessel disease, STEMI, and the SXscore

That patients with multivessel coronary artery disease have worse outcome when compared with single vessel disease in MI has been reported since the pharmacologic reperfusion era.[17] In the PPCI era, these patients have been shown to achieve less ST-segment recovery, a sign of myocardial reperfusion in a substudy of the CADILLAC trial.[6] In this substudy, 1-year mortality and MACE rates also differed between patients with single-, double-, and triple-vessel disease, and presence of the latter was the strongest among classical candidate predictors of outcome. The concomitant presence of a CTO in a vessel other than the IRA has been shown to be a considerably more important risk factor than the presence of multivessel disease alone in a study by van der Schaaf et al.[7] In

Table V. Hazard ratios from multivariate analysis of TIMI risk score and SXscore with value of model improvement for mortality and MACE

End point	Mortality		MACE	
Risk score	**HR (95%CI)**	***P***	**HR (95%CI)**	***P***
TIMI score	1.41 (1.29-1.55)	<.01	1.32 (1.22-1.43)	<.01
Model improvement by adding SXscore I to TIMI		.04*		<.01*
SXscore I	1.52 (1.03-2.23)	.04	1.63 (1.17-2.27)	.04
TIMI score	1.42 (1.29-1.55)	<.01	1.32 (1.22-1.43)	<.01
Model improvement by adding SXscore II to TIMI		.04*		<.01*
SXscore II	1.51 (1.03-2.21)	.03	1.63 (1.18 – 2.26)	<.01

HR, Hazard ratios; *CI*, confidence intervals.
*By omnibus test of model coefficients.

the present study, the mortality rate was highest in the highest tertile of SXscore, which predominantly included patients with 3-vessel disease and the largest number of CTOs. With the additional information about the nature of the lesions in multivessel disease subjects, the SXscore may be a better predictor than mere numeration of the vessels involved.

Implications for clinical practice

In patients undergoing PPCI for acute STEMI, quantification of the presence, severity, and complexity of coronary vessel disease by the SXscore is a useful tool in determining short-term and long-term outcome independently of any other clinical and angiographic and procedural characteristics. Patients in the higher tertiles are at high risk and may need more intensive supportive and interventional management to improve their event-free survival.

Implications for PCI trials

In "all comer" revascularization trials that include patients with a spectrum of coronary disease and patients treated for acute STEMI, the SXscore seems a useful tool in addition to the classical risk factors that ensure comparison of equal coronary disease anatomy between the cohorts being investigated.

Limitations

Although data were acquired prospectively, the study has a retrospective design and is in fact a registry analysis and therefore suffers from limitations. Data on enzymatic or other imaging-derived infarct size quantification were not available in all patients. Also, MBG and ST-segment resolution as markers of reperfusion could not be determined in all patients, and we used corrected TIMI frame count instead. These could not be incorporated into the models, and whether these would be better predictors than the SXscore remains unexplored.

Conclusion

The SXscore derived from angiography after during PPCI predicts long-term mortality and MACE in patients with STEMI. The score is relatively easy to obtain and has a moderate reproducibility, making it a clinically useful tool.

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5.7

Usefulness of the SYNTAX Score to Predict 'No Reflow' in Patients Treated with Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction.

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Am J Cardiol. 2012 Mar 1;109(5):601-6.

Usefulness of the SYNTAX Score to Predict "No Reflow" in Patients Treated With Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction

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The no-reflow phenomenon has been shown to have a significant effect on clinical outcomes in patients with acute ST-segment elevation myocardial infarction. Angiographic features incorporated in the SYNTAX Score (SXScore) obtained on diagnostic angiography during primary percutaneous coronary intervention (PPCI) may be associated with the occurrence of myocardial no-reflow. The aim of this study was to assess the ability of the SXScore to predict no-reflow during PPCI. The SXScore was applied to 669 consecutive patients presenting with acute ST-segment elevation myocardial infarction from November 2006 to February 2008. Angiographic analysis of the PPCI procedure was used to determine no-reflow. The median SXScore was 16 (range 9.5 to 23). No-reflow occurred in 77 patients (12%). On univariate logistic regression analysis, the SXScore showed a strong association (for each 10-unit increase in SXScore, odds ratio 1.42, 95% confidence interval 1.16 to 1.76, $p < 0.001$). On multivariate logistic regression in a model including clinical variables, SXScore was an independent predictor of no-reflow (odds ratio 1.29, 95% confidence interval 1.02 to 1.63, $p < 0.001$). Classification and regression tree analysis identified SXScore >21 as the best cutoff, with patients having double the risk for no-reflow compared to those with SXScore ≤ 21 (events 9% vs 18%, $p = 0.006$). In conclusion, the SXScore obtained in the diagnostic phase of PPCI for acute ST-segment elevation myocardial infarction can identify patients at risk for developing no-reflow. **(Am J Cardiol 2012;109:601–606)**

Myocardial no-reflow after primary percutaneous coronary intervention (PPCI) is associated with a increased incidence of clinical events and a poor survival rate after acute ST-segment elevation myocardial infarction (STEMI).[1,2] Patients at high risk for no-reflow include older subjects, those with previous coronary artery bypass surgery, and those presenting with higher Killip classes and longer ischemic times. Angiographic characteristics of patients with STEMI at higher risk for subsequent no-reflow include occlusion of the infarct-related artery (IRA), a high thrombus burden, saphenous graft as the culprit vessel, and multivessel disease.[3] Such angiographic characteristics can be quantified by the SYNTAX Score (SXScore).[4] The SXScore obtained in the diagnostic phase of PPCI, incorporates information including the patency of the IRA, the area of myocardium at risk supplied by the culprit vessel at the level of occlusion, as well as information on the complexity of the lesion and extent and severity of coronary artery disease.[5] Patients with STEMI with high SXScores are at increased risk for adverse events, including mortality, and the prognostic value of the score is independent and additive to other risk scores based on clinical variables such as the Thrombolysis In Myocardial Infarction (TIMI) and Primary Angioplasty in Myocardial Infarction (PAMI) scores.[4,6–8] The mechanisms that relate a high SXScore to adverse cardiovascular events in this patient population are unclear and may in part be mediated by a higher rate of failure to achieve adequate myocardial reperfusion during PPCI. We hypothesized that with its additional angiographic characterization of patients presenting for PPCI, the SXScore can stratify patients at risk for developing myocardial no-reflow.

Methods

From November 2006 to February 2008, 736 consecutive patients who underwent PPCI for STEMI at our institution were screened for inclusion in the MI SXScore study.[4] All patients in the referral area of the Thoraxcenter, Erasmus Medical Center (Rotterdam, The Netherlands) who had symptoms of acute myocardial infarction (<12 hrs duration) were assessed clinically and using 12-lead electrocardiography by paramedical personnel or peripheral hospital medical staff members. Pretreatment with aspirin, clopidogrel, and heparin was administered before hospital admission. Urgent diagnostic angiography was followed by PPCI using standard techniques. Drug-eluting stents were implanted as the first-line choice of stent. Treatment for complications such as cardiogenic shock and cardiac arrest was performed according to guidelines.

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The SXScore was calculated as previously described.[4] In short, SXScore I was obtained from the diagnostic angiogram before any intervention, and SXScore II was calculated after wiring the IRA. The principal difference between SXScore I and SXScore II is a reduction of 5 points attributed to total occlusion of the IRA in patients in whom simple wiring of the occluded vessel resulted in restoration of TIMI flow of 2 or 3. Patients with previous coronary artery bypass grafting in whom the SXScore could not be calculated were excluded from the study. All coronary lesions with diameter stenoses ≥50% in vessels ≥1.5 mm were scored using the SXScore algorithm, which is available at http://www.syntaxscore.com. The SXScore for each patient was calculated by a team of 2 interventional cardiologists. In case of disagreement with regard to the significance of a lesion, quantitative coronary angiography was applied, and the lesion was included if it was ≥50% stenosis. On agreement between the 2 cardiologists, the data were entered into a dedicated software program.

The investigators calculating the SXScores were blinded to patients' clinical characteristics. The scoring was done prospectively at each stage so that the investigators were blinded to the next-stage film, to the procedural data, and to the clinical outcomes. No changes in values were allowed once scores were assigned. In this study, SXScore I was the score of interest, because we hypothesized that the score obtained in the diagnostic or preintervention phase is associated with no-reflow. Therefore, unless stated otherwise, "SXScore" refers to SXScore I.

TIMI flow and corrected TIMI frame count were assessed as previously reported.[9] Myocardial blush grade was assigned as described by van 't Hof et al.[10] Angiographic epicardial artery no-reflow was defined as an acute temporary or persistent reduction in coronary flow (TIMI flow grade 0 or 1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the target lesion. Slow flow was recorded if there was a temporary reduction from TIMI flow grade 3 to grade 2. Distal embolization was defined as visible downstream movement of a contrast filling defect from the site of the culprit lesion. Distal occlusion was defined as a distal filling defect with an abrupt "cutoff" in one of the peripheral coronary artery branches of the infarct-related vessel distal to the site of angioplasty.

Survival data for all patients were obtained from the municipal registry. A health questionnaire was subsequently sent to all living patients with specific questions on re-admission and major adverse cardiac events. For patients with adverse events at other centers, medical records, discharge summaries and, when necessary, angiographic films were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. Events were adjudicated by 2 experienced interventional cardiologists according to the following definitions. STEMI was diagnosed when patients had symptoms of acute myocardial infarction lasting ≥30 minutes and accompanied by >1-mm (0.1-mV) ST-segment elevation in ≥2 contiguous leads and later confirmed by creatine kinase and creatine kinase-MB increases and/or troponin increase. Target vessel revascularization was defined as any percutaneous coronary intervention of the index IRA. Major adverse cardiac events were defined as a composite of death, recurrent myocardial infarction, and target vessel revascularization.

Table 1
Baseline and presenting characteristics of patients with acute myocardial infarction according to low or high SYNTAX Score

Variable	Lower SXScore (<16) (n = 332)	Higher SXScore (≥16) (n = 337)	p Value
Age (years)	63 ± 13	67 ± 12	<0.01
Men	221 (67%)	248 (74%)	0.047
Diabetes mellitus	22 (7%)	41 (12%)	0.014
Type I	11 (3%)	17 (5%)	0.26
Type II	12 (4%)	25 (7%)	0.03
Hypertension	101 (30%)	123 (37%)	0.096
Hypercholesterolemia*	64 (19%)	76 (23%)	0.3
Smokers			
Current	155 (47%)	125 (37%)	0.012
Former	46 (14%)	45 (13%)	0.036
Renal failure†	4 (1%)	14 (4%)	0.018
Family history of coronary artery disease	121 (36%)	89 (26%)	<0.01
Body mass index (kg/m^2)	27 ± 4	27 ± 4	0.74
Previous myocardial infarction	25 (8%)	60 (18%)	<0.01
Previous percutaneous coronary intervention	30 (9%)	34 (10%)	0.64
Symptom onset–to–balloon time >90 minutes	257 (84%)	264 (87%)	0.27
Out-of-hospital cardiac arrest	13 (4%)	18 (5%)	0.38
Pulse rate (beats/min)	77 ± 16	80 ± 19	0.037
Blood pressure (mm Hg)			
Systolic	124 ± 26	123 ± 27	0.29
Diastolic	75 ± 14	75 ± 16	0.45
Cardiogenic shock	19 (6%)	36 (11%)	0.02
Killip class 2–4	18 (5%)	34 (10%)	0.024

Data are expressed as mean ± SD or as number (percentage); percentages are rounded.

* Fasting total serum cholesterol level >5.5 mmol/L (210 mg/dl) or use of lipid-lowering therapy.

† Creatinine clearance <70 ml/min.

The no-reflow phenomenon was defined by ≥1 of the following: final TIMI flow grade <3, final myocardial blush grade <2, temporary epicardial coronary no-reflow, distal coronary occlusion, and a final corrected TIMI frame count of >100 frames/s.[9]

Continuous variables are expressed as mean ± SD or as medians and interquartile ranges, and categorical variables are presented as absolute numbers and percentage. Continuous variables were compared using Student's unpaired *t* tests or Mann-Whitney nonparametric U tests. Categorical variables were compared using chi-square statistics or Fisher's exact tests as appropriate. Observed unadjusted and adjusted measures of association were obtained using logistic regression models and are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Separate logistic regression analyses were performed to identify independent predictors of no-reflow using all clinical variables. These univariate predictors were entered into a second logistic regression model to obtain the adjusted OR. The multivariate model consisted of SXScore and the clinical variables:

Table 2
Angiographic characteristics, procedural characteristics, and management of patients with acute myocardial infarction with low and high SYNTAX Scores

Variable	Lower SXScore (<16) (n = 332)	Higher SXScore (≥16) (n = 337)	p Value
Anterior STEMI	127 (38%)	177 (53%)	<0.001
Infarct-related coronary artery			
Left main	6 (2%)	36 (11%)	<0.01
Left anterior descending	111 (34%)	169 (50%)	<0.01
Left circumflex	63 (19%)	46 (14%)	0.06
Right	156 (47%)	119 (35%)	<0.01
Initial TIMI flow grade 0 or 1 in IRA	157 (48%)	253 (75%)	<0.01
Stent thrombosis (cause)	12 (4%)	13 (4%)	0.86
Number of diseased coronary arteries			
1	222 (67%)	59 (18%)	<0.01
2	91 (27%)	115 (34%)	0.06
3*	18 (5%)	163 (48%)	<0.01
Left main disease	6 (2%)	36 (11%)	<0.01
Chronic total occlusion	4 (1%)	42 (13%)	<0.01
Stent implantation	311 (94%)	305 (91%)	0.096
Balloon predilatation	60 (18%)	60 (17%)	0.91
Total stent length (mm)	28 (18–40)	30 (23–51)	<0.01
Stent diameter (mm)	3.0 ± 0.5	3.0 ± 0.5	0.83
Bifurcation treatment in IRA	47 (14%)	76 (23%)	<0.01
Balloon postdilatation	63 (19%)	61 (18%)	0.73
Thrombectomy	62 (19%)	62 (19%)	0.93
Glycoprotein IIb/IIIa inhibitors	73 (22%)	74 (22%)	0.99
Inotropic agents	14 (4%)	17 (5%)	0.61
Intra-aortic balloon pump	15 (5%)	30 (9%)	0.024
Multivessel stenting	26 (8%)	43 (13%)	0.036
Final TIMI flow grade 0 or 1	7 (2%)	21 (6%)	<0.01
Corrected TIMI frame count at end (frames/s)	24 (16–36)	26 (18–40)	0.052
Myocardial blush grade 0 or 1	3 (1%)	19 (6%)	<0.01

Data are expressed as mean ± SD, as median (interquartile range), or as number (percentage); percentages are rounded.
* Includes patients with left main disease plus 1-vessel disease.

age, gender, out-of-hospital cardiac arrest, Killip class, cardiogenic shock, pulse rate, and blood pressure. The effects of procedural characteristics, including thrombus aspiration, glycoprotein IIb/IIIa inhibitor use, and balloon predilatation and postdilatation, on no-reflow and on the relation of SXScore and no-reflow were further explored using a Cox regression model including these variables. Classification and regression tree analysis was performed to determine the best SXScore value cutoff that stratified patients at high versus low risk for developing no-reflow. To assess which of the angiographic characteristics best affected the association of SXScore and no-reflow, a separate logistic regression analysis in a multivariate model with the angiographic variables IRA, TIMI flow before wiring, thrombus grade after wiring, number of vessels diseased, chronic total occlusion, and bifurcation was performed.

The cumulative incidence of adverse events according to the presence of no-reflow was estimated according to the Kaplan-Meier method, and curves were compared using the log-rank test. A p value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, Illinois).

Table 3
Differences in angiographically detected complications between patients presenting with low versus high SYNTAX Scores

Angiographic Complication	Lower SXScore (<16) (n = 332)	Higher SXScore (≥16) (n = 337)	p Value
Dissection	17 (5%)	12 (4%)	0.322
Perforation	6 (2%)	4 (1%)	0.51
Distal embolization	16 (5%)	15 (5%)	0.82
Slow flow	7 (2%)	14 (4%)	0.13
Angiographic no-reflow*	6 (2%)	11 (3%)	0.23
TIMI flow grade 0 or 1 final*	7 (2%)	21 (6%)	<0.001
Corrected TIMI frame count >100 frames/s*	5 (2%)	24 (7%)	<0.001
Myocardial blush grade 0 or 1*	3 (1%)	19 (6%)	<0.001
Composite no-reflow	29 (9%)	48 (14%)	0.026

Percentages are rounded.
* Parameters included in composite end point no-reflow in this study.

Table 4
Predictors of myocardial no-reflow on multivariate analysis in model with clinical characteristics and SYNTAX Score

Predictor	OR (95% CI)	p Value
SXScore (per 10-unit increase)	1.29 (1.02–1.63)	<0.001
Age (per 10-year increase)	1.23 (0.99–1.54)	0.058
Pulse rate (per 10 beats/min increase)	1.02 (1.01–1.03)	0.012

Results

From the initial 736 patients screened, 27 were excluded because of unavailability of a complete diagnostic coronary angiogram, and 21 were excluded because they had undergone previous coronary artery bypass grafting. Survival status and follow-up could not be obtained in 19 patients. Thus, the final number of patients included in our analysis was 669. The median SXScore was 16 (range 9.5 to 23). Differences in the baseline clinical characteristics in patients with low and high SXScores are listed in Table 1. Patients with a higher SXScores (≥16) were older, more often male, and more often had type 2 diabetes, and smoking and previous myocardial infarction were more prevalent in this group. Patients presenting in the acute phase with higher pulse rates, cardiogenic shock, and higher Killip classes more often had higher SXScores.

Table 2 lists the differences in angiographic and procedural characteristics between patients with low and high SXScores. The left main stem and the left anterior descending coronary artery were more commonly the culprit vessels in patients with high SXScores, whereas the left circumflex coronary artery and the right coronary artery were more commonly the IRAs in low-SXScore patients. Furthermore, the IRA more often had poor anterograde flow (TIMI grade

Table 5
Angiographic predictors of no-reflow

Predictor	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Infarct-related coronary artery				
Left main stem	3.46 (1.69–7.08)	0.001	2.42 (0.96–6.09)	0.06
Left anterior descending	1.50 (0.93–2.41)	0.098	1.37 (0.80–2.35)	0.25
Left circumflex	0.41 (0.17–0.95)	0.037	0.56 (0.22–1.43)	0.22
Right	0.96 (0.59–1.56)	0.86		
Number of coronary arteries with significant disease				
2	0.71 (0.41–1.23)	0.218	—	—
3	1.54 (0.94–1.54)	0.094	1.18 (0.63–2.22)	0.6
Chronic total occlusion	1.99 (0.92–4.29)	0.081	1.03 (0.40–2.65)	0.95
Bifurcation at IRA	0.80 (0.42–1.53)	0.497	—	—
TIMI flow before wiring	0.66 (0.53–0.82)	<0.001	0.71 (0.56–090)	0.004
Thrombus grade after wiring	1.73 (1.43–2.10)	<0.001	1.60 (1.32–1.95)	<0.001

The univariate model consists of the angiographic parameters described in the text. The multivariate model contains angiographic parameters that were significant ($p < 0.05$) on univariate analysis.

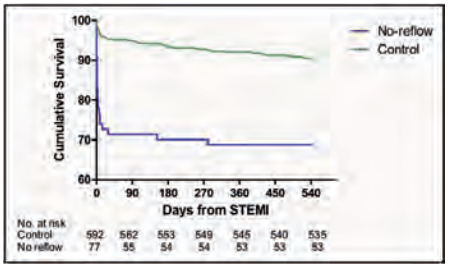

Figure 1. Kaplan-Meier curves of survival in patients with and without no-reflow (control). At 18-month follow-up, the mortality rate was 31% versus 10% (log-rank $p < 0.001$).

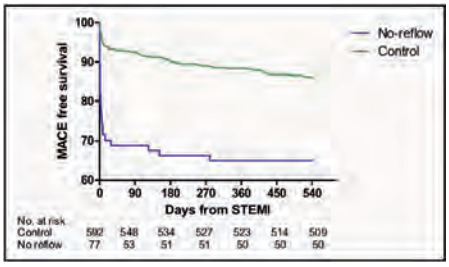

Figure 2. Kaplan-Meier curves of survival free of major adverse cardiac events (MACE; including death, repeat myocardial infarction, and target vessel revascularization) in patients with and without no-reflow. At 18-month follow-up, the MACE rate was 35% versus 14% (log-rank $p < 0.001$).

0 or 1) in patients with high SXScores. Multivessel disease, chronic total occlusions, and bifurcations were more often present in patients with higher scores, and this reflected a higher rate of multivessel and bifurcation stenting and a longer total stent length implanted. There was no difference in the procedural use of thrombectomy, glycoprotein IIb/IIIa inhibitors, or balloon predilatation or postdilatation between the 2 groups. The use of an intra-aortic balloon pump was necessary in twice as many patients with SXScores ≥ 16 compared with those with scores < 16.

The no-reflow phenomenon occurred in 77 patients (12%) included in the analysis. The components used to define the composite end point are listed in Table 3. On univariate logistic regression analysis, the SXScore showed a strong association with no-reflow (for each 10-unit increase in SXScore, unadjusted OR 1.42, 95% CI 1.16 to 1.76, $p < 0.001$). The other univariate predictors of no-reflow were age, gender, out-of-hospital arrest, Killip class, shock, pulse rate, and blood pressure. After adjusting for these predictors in multivariate logistic regression, the SXScore was an independent predictor of no-reflow (per 10-unit increase in SXScore, adjusted OR 1.29, 95% CI 1.02 to 1.63, $p < 0.001$; Table 4).

Classification and regression tree analysis identified SXScore >21 as the best cutoff, with patients having twice the risk for no-reflow compared to those with SXScores ≤ 21 (events 9% vs 18%, $p = 0.006$). The relation of SXScore II was also explored in a separate but similar multivariate model, and as with SXScore I, it also showed an independent association with no-reflow (OR 1.53, 95% CI 1.24 to 1.89, $p < 0.001$; adjusted OR 1.29, 95% CI 1.03 to 1.63, $p = 0.009$). Assessment of the relation of angiographic characteristics and no-reflow is listed in Table 5. Angiographic characteristics that were independent predictors of no-reflow on multivariate analysis included left main stem involvement, TIMI flow grade on presentation, and thrombus grade after wiring. Of the procedural characteristics, only patients with predilatation had a trend toward a higher risk for developing no-reflow (OR 1.7, 95% CI 0.99 to 2.99, $p = 0.054$). Adjustment for predilatation by entering it in a multivariate model did not significantly influence the OR of the SXScore for no-reflow (OR 1.29, 95% CI 1.03 to 1.63, $p = 0.029$). The Kaplan-Meier curves in Figures 1 and 2 show the increased mortality rate (31% vs 10%, $p < 0.001$) and rate of major

adverse cardiac events (35% vs 14%, p <0.001) at 18 months in patients who developed no-reflow.

Discussion

The SXScore is an independent predictor of myocardial no-reflow in patients with STEMI. An SXScore >21 carries a double risk for developing no-reflow. Myocardial no-reflow carries a poor prognosis and an increased mortality rate. Thus, intraprocedural measures that can prevent this phenomenon would be especially beneficial in patients at high risk as identified by the SXScore. Preventive measures may include pharmacologic agents such as glycoprotein IIb/IIIa inhibitors, adenosine, nitroprusside, and nicorandil as well as mechanical measures such as thrombus aspiration.

In this study, no-reflow was identified by changes in TIMI flow in the epicardial artery, which directly affects myocardial perfusion, as well as more direct imaging of myocardial perfusion as measured by the myocardial blush grade. TIMI flow grade is a crude but accurate indicator for myocardial reperfusion if this is suboptimal (i.e., <3). The corrected TIMI frame count adds more sensitivity for categorizing no-reflow for patients in whom TIMI flow ≥2 is achieved. A cutoff of 100 frames/s was chosen on the basis of data from previous studies.[9]

One of the major components of the SXScore that enhances its predictive value on the eventual achievement of microvascular perfusion is the patency (or otherwise) of the IRA. An occluded IRA has been shown to be associated with a worse postprocedural myocardial perfusion (TIMI myocardial perfusion grade of 3, 54.9% vs 18.7%, p <0.0001). Patency of the IRA often signifies earlier spontaneous reperfusion, which reduces the actual ischemic time. As a result, infarction size is limited, and improvement in the left ventricular ejection fraction is greater in such patients, which is reflected in improved 1-year outcomes.[11] The SXScore adds 5 points if the IRA has TIMI grade 0 or 1 flow, reflecting the importance of IRA patency in no-reflow and short- and long-term mortality. Poor anterograde flow is also often associated with a higher thrombus load, and this in turn has been associated with slow flow and the no-reflow phenomenon.[12] Embolization of atherothrombotic material has been implicated as an important pathophysiologic mechanism leading to poor microvascular perfusion. Antithrombotic, thrombolytic or thrombus aspiration have all been shown to reduce the incidence of the no-reflow phenomenon.[13–15] Given the associated risks associated with these adjunctive therapeutic measures, such as bleeding and cerebrovascular accidents, limiting use in patients who may benefit most from these treatments is desirable.

The difference in the myocardial area at risk is also an important component of the SXScore, and the different weighting given to the coronary arteries does influence the occurrence of no-reflow. Although infarction in the left circumflex coronary artery is less likely to result in detectable no-reflow, that in the proximal left coronary artery, especially the left main stem, carries a 3.5-fold risk for no-reflow.

In the present study, the presence of a chronic total occlusion and 3-vessel disease had a non-significant trend of association with no-reflow. Although the lack of statistical significance can be attributed to a lack of power, the incorporation of these parameters in the SXScore ensures appropriate consideration of these parameters in the risk stratification of no-reflow. In contrast, chronic total occlusion and multivessel disease are not as important as TIMI flow and the location of the occlusion. No-reflow as an angiographic marker of myocardial perfusion focuses on the territory at risk, which although as expected is affected mostly by the characteristics pertinent to the IRA, can be affected by the presence and extent of disease elsewhere. Diffuse disease often signifies an impaired microcirculatory resistance index.[16] Moreover, collateral circulation to the microvascular bed, which is considered protective, would be poorly developed or insufficient if the contributing artery is also diseased.

Although observers scoring the SXScore were blinded to the next-step angiographic film and changes to the score were not allowed after film review, bias of scoring no-reflow in patients with high SXScores may still have affected our observations. However the post hoc analytic nature of the study derived from the MI SXScore study database guarantees to a limited extent the validity of our findings. The relation of the SXScore and the outcome is unlikely to have been influenced by operator-dependent choice of treatment. In fact, in our study, patients with higher scores were not treated differently, especially with regard to predilatation, stenting, thrombectomy, and glycoprotein IIb/IIIa inhibitor use. In determining no-reflow, we chose to use only angiographic parameters. ST-segment resolution as another measure of no-reflow was not available in all patients. Moreover, we could not determine the effect of the SXScore and the occurrence of no-reflow on final infarct size, because neither enzymatic infarct size nor infarct size by noninvasive imaging modalities was available in all patients. Nonetheless, the SXScore has significant predictive value for the occurrence of angiographically defined no-reflow.

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5.8

The MI SYNTAX Score for Risk Stratification in Patients Undergoing Primary Percutaneous Coronary Intervention for Treatment of Acute Myocardial Infarction: a substudy of the COMFORTABLE AMI trial.

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The MI SYNTAX score for risk stratification in patients undergoing primary percutaneous coronary intervention for treatment of acute myocardial infarction: A substudy of the COMFORTABLE AMI trial

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ABSTRACT

Background: To investigate the performance of the MI Sxscore in a multicentre randomised trial of patients undergoing primary percutaneous coronary intervention (PPCI).

Methods and results: The MI Sxscore was prospectively determined among 1132 STEMI patients enrolled into the COMFORTABLE AMI trial, which randomised patients to treatment with bare-metal (BMS) or biolimus-eluting (BES) stents. Patient- (death, myocardial infarction, any revascularisation) and device-oriented (cardiac death, target-vessel MI, target lesion revascularisation) major adverse cardiac events (MACEs) were compared across MI Sxscore tertiles and according to stent type.

The median MI SXscore was 14 (IQR: 9–21). Patients were divided into tertiles of $Sxscore_{low}$ (≤ 10), $Sxscore_{intermediate}$ (11–18) and $Sxscore_{high}$ (≥ 19). At 1 year, patient-oriented MACE occurred in 15% of the $Sxscore_{high}$, 9% of the $Sxscore_{intermediate}$ and 5% of the $Sxscore_{low}$ tertiles ($p < 0.001$), whereas device-oriented MACE occurred in 8% of the $Sxscore_{high}$, 6% of the $Sxscore_{intermediate}$ and 4% of the $Sxscore_{low}$ tertiles ($p = 0.03$). Addition of the MI Sxscore to the TIMI risk score improved prediction of patient- (c-statistic value increase from 0.63 to 0.69) and device-oriented MACEs (c-statistic value increase from 0.65 to 0.70). Differences in the risk for device-oriented MACE between BMS and BES were evident among $Sxscore_{high}$ (13% vs. 4% HR 0.33 (0.15–0.74), $p = 0.007$ rather than those in $Sxscore_{low}$: 4% vs. 3% HR 0.68 (0.24–1.97), $p = 0.48$) tertiles.

Conclusions: The MI Sxscore allows risk stratification of patient- and device-oriented MACEs among patients undergoing PPCI. The addition of the MI Sxscore to the TIMI risk score is of incremental prognostic value among patients undergoing PPCI for treatment of STEMI.

1. Introduction

The risk of adverse events among patients presenting with acute myocardial infarction has been thoroughly assessed by means of clinical variables incorporated into the TIMI risk score during the thrombolysis

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era [1,2]. The advent of primary percutaneous coronary intervention (PPCI) as the preferred reperfusion strategy among patients with ST-segment elevation myocardial infarction (STEMI) identified angiographic variables obtained at the time of the intervention to be of additional prognostic significance in observational studies [3].

The SYNTAX score (Sxscore) quantifies angiographic characteristics and disease complexity among patients undergoing PCI and has been shown to predict MACE during follow-up in patients with stable and unstable coronary artery diseases [4]. Among patients with stable coronary artery disease, the combined use of clinical and angiographic variables in the global risk assessment further improved the predictive value [5]. Among STEMI patients, the addition of angiographic characteristics quantified by the MI Sxscore improved the TIMI risk model for prediction of major adverse cardiac events in a recent study including observational data from 669 consecutive STEMI patients [6]. The performance of such a model in all-comer STEMI trials remains to be examined. We therefore validated the MI Sxscore in a contemporary, multicenter trial of STEMI patients undergoing primary PCI, the COMFORTABLE AMI trial [7].

2. Methods

2.1. Study population

The COMFORTABLE AMI trial included patients 18 years of age or older who had a history of chest pain of more than a 10 min duration and associated ST segment elevation of >1 mm in ≥2 contiguous leads, new left bundle branch block or true posterior MI, who underwent primary percutaneous coronary intervention (PCI) within 24 h of symptom onset. In addition, there was angiographic presence of at least one acute infarct related artery (IRA) with one or multiple coronary artery lesions in a native coronary artery with a diameter between 2.25 and 4.0 mm, which could be treated with one or multiple stents. Exclusion criteria included use of vitamin K antagonists, mechanical complications of myocardial infarction, acute myocardial infarction secondary to stent thrombosis (ST), planned surgery within 6 months of PCI unless dual antiplatelet therapy could be maintained throughout the peri-surgical period and non-cardiac comorbid conditions with life expectancy <1 year. Further study details are described in detail elsewhere [7,8].

Angiography was digitally recorded and analysed in a central core laboratory. The MI Sxscore was assessed by experienced analysts using the web based programme www.syntaxscore.com as previously described. Angiographic documentation of patients included in the COMFORTABLE AMI trial was scored as described previously. In brief, the MI Sxscore for each patient was calculated by two independent and blinded, interventional cardiologists, taking into account the patency of the infarct related artery. An infarct related artery (IRA) with TIMI flow of 0 or 1 was scored as a total occlusion with thrombus. The CABG Sxscore was calculated by determining the standard Sxscore in native coronary vessels and subtracting points based on the importance of the diseased coronary artery segment (Leaman score) that are supplied by a functioning bypass graft. Points relating to intrinsic coronary artery disease, such as bifurcation disease or calcification, remained unaltered [9]. The interobserver and intraobserver variabilities of the Sxscoring team were previously reported as moderate (kappa statistic 0.56) and substantial (kappa statistic 0.70). The trial randomly assigned 1161 patients with acute ST-segment elevation myocardial infarction (STEMI) to treatment with biolimus-eluting stents with a biodegradable polymer (BioMatrix; Biosensors Inc., Morges, Switzerland) and bare-metal stents (BMSs) using the same platform design (Gazelle, Biosensors Inc., Morges, Switzerland).

2.2. Primary and secondary endpoints

The primary clinical end points of this study were patient-oriented MACE, defined as the composite of all-cause death, any reinfarction (MI) and any revascularisation, and device-oriented MACE, defined as a composite of cardiac death, target vessel reinfarction (TV-MI) and ischaemia-driven target-lesion revascularisation (TLR). Secondary endpoints included all-cause and cardiac deaths, target-vessel reinfarction (TV-MI), any reinfarction, composite of death or recurrent MI, ischaemia-driven target-lesion (TLR) and target vessel revascularisation (TVR), and ARC-defined definite and definite or probable stent thrombosis (ST) [10]. Details of the definitions of the primary and secondary endpoints used for adjudication of events by the independent clinical events committee (CEC) are reported elsewhere [8].

2.3. Statistical analysis

Continuous variables are presented as mean ± 1SD or as median and interquartile ranges. Categorical variables are presented as counts and percentages. To characterise differences between different Sxscores, the study cohort was divided into three groups according to MI Sxscore tertiles; $Sxscore_{high}$, $Sxscore_{intermediate}$ and $Sxscore_{low}$. Analyses of variance (ANOVA, for continuous variables), Kruskal–Wallis tests (for non-parametric variables) and Chi-squares tests (for categorical variables) were used to describe differences between the 3 groups. Comparisons involving the 2 stents were performed using unpaired t-tests.

Cox regression analysis was used to determine the risk ratio of Sxscore tertiles for the primary endpoint as well as individual endpoints at 30 days and 1 year. This was performed for the whole cohort as well as individually for each of the randomised groups

Table 1
Baseline characteristics of the COMFORTABLE AMI population according to SYNTAX score tertiles.

	Baseline characteristics			
	Syntax score			
	Low (0–10) N = 394	Intermediate (11–18) N = 374	High (19–52) N = 364	p value[a]
Baseline characteristics				
Age, years	58.7 ± 12.2	60.5 ± 11.0	62.6 ± 11.7	<0.001
Male gender	302 (77%)	297 (79%)	298 (82%)	0.21
Diabetes	47 (12%)	65 (17%)	58 (16%)	0.09
Insulin-dependent	8 (2%)	6 (2%)	11 (3%)	0.45
Hypertension	172 (44%)	178 (48%)	182 (50%)	0.21
Hypercholesterolaemia	224 (57%)	219 (59%)	194 (54%)	0.38
Smoker at any time	303 (77%)	293 (79%)	253 (71%)	0.02
Current smoker	209 (53%)	194 (52%)	157 (44%)	0.02
Ex-smoker	94 (24%)	99 (27%)	96 (27%)	0.61
Renal failure	65 (17%)	69 (19%)	69 (19%)	0.63
Family history of CAD	128 (33%)	122 (34%)	110 (31%)	0.68
Body mass index, kg/m^2	27.4 ± 4.4	27.2 ± 4.1	27.0 ± 4.3	0.46
Previous myocardial infarction	13 (3%)	22 (6%)	27 (7%)	0.04
Previous PCI	14 (4%)	16 (4%)	14 (4%)	0.87
Previous CABG	7 (2%)	5 (1%)	2 (1%)	0.33
Clinical presentation				
Time from symptom onset to balloon inflation, min	228.0 (159.0–354.0)	236.0 (163.5–392.0)	244.0 (170.0–400.0)	0.64
Resuscitation prior to hospital arrival	10 (3%)	6 (2%)	9 (2%)	0.61
Pulse rate, bpm	75.3 ± 15.1	76.0 ± 16.0	77.4 ± 16.9	0.20
Blood pressure, mm Hg				
Systolic	128.5 ± 22.6	131.4 ± 22.9	129.1 ± 23.5	0.19
Diastolic	77.5 ± 14.8	79.1 ± 14.2	77.9 ± 15.6	0.35
Cardiogenic Shock	0 (0%)	2 (1%)	10 (3%)	0.001
Killip class II, III or IV	20 (5%)	14 (4%)	39 (11%)	<0.001

Data is expressed in numbers and (percentages) or means ± 1 standard deviation. PCI = Percutaneous coronary intervention, CABG = coronary artery bypass.
[a] p value calculated using ANOVA for continuous variables or Kruskal–Wallis test for non-parametric variables and Chi-square test for categorical variables.

receiving BMS and the drug eluting stent. Event curves employing the Kaplan–Meier method were then generated to depict the differences across the MI Sxscore tertiles for the primary end point MACE and its components. To explore the effect of stratification in MI Sxscore tertiles, differential outcomes between BMS and biolimus-eluting stents were explored.

In a separate analysis, variables in the TIMI risk score including age >74, history of diabetes, hypertension or heart failure, systolic blood pressure <100 mm Hg, heart rate >100 beats per minute, Killip classes II–IV, body weight <67 kg, anterior STEMI and time to treatment of >4 h were used to assess the additional predictive value of the MI Sxscore as determined by the c-statistic. The performance of the model combining the TIMI risk score with the MI Sxscore in this all-comer randomised trial was compared to values achieved with the model studied using published previously data from an observational study. We used this comparison as a method of validation for the model [6].

All statistical tests were 2-tailed, and p values were significant at <0.05. Analysis was performed using STATA version 12.1 (StataCorp).

3. Results

Complete angiographic analysis of the MI Sxscore was performed in 1132 of 1161 patients enrolled in the COMFORTABLE AMI trial. The median (interquartile range) MI Sxscore of the entire patient cohort was 14 [9–21], and was not different between patients randomised to BES and BMS (15.1 vs. 14.8, p = 0.54). The $Sxscore_{low}$ tertile was composed of 394 patients with scores up to 10, the $Sxscore_{intermediate}$ tertile of 374 patients with scores ranging from 11 to 18, and the $Sxscore_{high}$ tertile of 364 patients with scores ranging from 19 to 52. Baseline clinical characteristics according to MI Sxscore tertiles are summarised in Table 1. Patients with higher MI Sxscores were older, and had a higher prevalence of diabetes, history of previous myocardial infarction, cardiogenic shock and signs of heart failure.

Angiographic characteristics across the three tertiles are summarised in Table 2. Patients with higher MI Sxscores were more likely to present with anterior myocardial infarction with the left anterior descending coronary artery (LAD) as the infarct related artery (IRA), an occluded IRA or a reduced TIMI 0/1 flow. Similarly, a higher number of stents was implanted into longer coronary artery segments, and there were more bifurcations and a higher number of treated vessels among patients in the $Sxscore_{high}$ group.

While a final post-procedure TIMI flow of 0/1 was present in only 1% of the $Sxscore_{high}$ group, a poor myocardial blush grade (MBG 0/1) was present in 9% of patients in this group, which was more frequent than that in the other tertiles (3% in the $Sxscore_{intermediate}$ group and 2% in the $Sxscore_{low}$ group, <0.001). The peak creatinine kinase also correlated with higher tertiles of MI Sxscore (Fig. 1).

We observed no differences in medication intake across the MI Sxscore tertiles at 1 year except for oral anticoagulants, which were more frequently prescribed in the highest MI Sxscore tertile.

Similar differences in baseline and procedural characteristics across MI Sxscore tertiles were observed in an analysis stratified according to stent type (Supplementary Tables 1 and 2 for bare metal stents and Supplementary Tables 3 and 4 for biolimus eluting stents).

Table 2
Angiographic and procedural characteristics of the COMFORTABLE AMI according to Sxscore tertiles.

	SYNTAX score			
	Low (0–10) N = 394	Intermediate (11–18) N = 374	High (19–52) N = 364	p value[a]
Angiographic characteristics pre-procedural				
Anterior STEMI	99 (25%)	112 (30%)	206 (57%)	<0.001
Infarct related artery, IRA				
Left main	1 (0%)	1 (0%)	3 (1%)	0.41
Left anterior descending	120 (31%)	124 (33%)	220 (60%)	<0.001
Left circumflex	70 (18%)	73 (20%)	46 (13%)	0.033
Right coronary	214 (54%)	194 (52%)	124 (34%)	<0.001
TIMI 0 or 1	165 (42%)	274 (73%)	305 (84%)	<0.001
Treated vessels incl. IRA[b]				0.012
1-Vessel disease	381 (97%)	357 (95%)	334 (92%)	0.005
2-Vessel disease	12 (3%)	15 (4%)	29 (8%)	0.005
3-Vessel disease	0 (0%)	2 (1%)	1 (0%)	0.36
Left main disease	1 (0%)	1 (0%)	3 (1%)	0.41
Procedural characteristics				
Number of stents implanted in IRA	1.3 ± 0.5	1.5 ± 0.8	1.6 ± 0.8	<0.001
Total stent length in IRA, mm	23.9 ± 10.8	28.3 ± 14.4	30.0 ± 14.7	<0.001
Average stent diameter in IRA, mm	3.2 ± 0.5	3.2 ± 1.4	3.2 ± 0.4	0.37
Bifurcation treatment in IRA	26 (7%)	29 (8%)	44 (12%)	0.02
Thrombectomy	240 (61%)	226 (60%)	240 (66%)	0.24
GP IIb/IIIa Inhibitors	179 (45%)	173 (46%)	173 (48%)	0.85
Intra-aortic balloon pump	3 (1%)	7 (2%)	18 (5%)	0.001
Multivessel stenting	12 (3%)	16 (4%)	30 (8%)	0.004
Angiographic characteristics post-procedural				
TIMI 0 or 1	1 (0%)	0 (0%)	3 (1%)	0.15
Corrected TIMI frame count at end procedure, fps	24.9 ± 15.3	25.7 ± 20.5	26.4 ± 21.3	0.61
Myocardial blush grade 0 or 1	9 (2%)	12 (3%)	31 (9%)	<0.001
Follow-up				
Complete revascularisation within 90 days[b]	3 (1%)	11 (3%)	16 (4%)	0.007
Medication at 1 year				
Aspirin	365 (97%)	340 (97%)	326 (97%)	0.83
Clopidogrel	171 (46%)	160 (45%)	147 (44%)	0.84
Prasugrel	132 (35%)	137 (39%)	129 (38%)	0.53
Beta-blocker	290 (78%)	280 (80%)	273 (81%)	0.47
ACE-inhibitors	219 (59%)	216 (61%)	223 (66%)	0.10
Statins	347 (93%)	328 (93%)	307 (91%)	0.64
Oral anticoagulant	8 (2%)	7 (2%)	19 (6%)	0.008

Data is expressed in numbers and (percentages), mean ± 1 standard deviation or median and (interquartile range). STEMI = ST elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction; GP = glycoprotein; PCI = percutaneous coronary intervention CABG = coronary artery bypass graft; and IRA = infarct related artery.

[a] p value calculated using ANOVA for continuous variables and Chi-square test for categorical variables.

[b] n = 28 requiring PCI and n = 2 requiring coronary artery bypass graft.

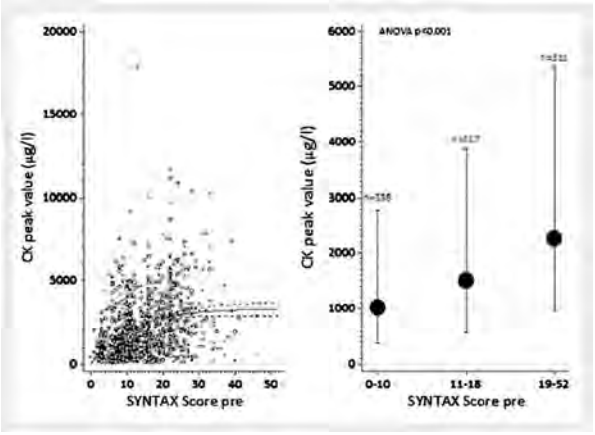


Fig. 1. SYNTAX score and infarct size based on peak creatinine kinase values. The left plot shows the relation of peak enzyme release and Sxscore while the right plots show the peak enzymes in tertiles of Sxscore.

3.1. Clinical outcomes

Clinical outcomes stratified according to the MI Sxscore tertiles are shown in Tables 3 (30 days) and 4 (1 year). Patient-oriented MACE (Fig. 2) was more common in the $Sxscore_{high}$ than in the $Sxscore_{low}$ tertiles at 30 days and 1 year (HR 2.38, 95% CI (1.26–4.49), p = 0.007). Device-oriented MACE (Fig. 3) was also more frequent in the $Sxscore_{high}$ than in the $Sxscore_{low}$ tertiles at 30 days and 1 year (HR 3.05, 95% CI 1.02–5.10, p < 0.001). Patients with MI Sxscores of ≤10 had a rate of device-related MACE as low as 2% at 30 days and 4% at 1 year. Conversely, rates of device-oriented MACE among patients with a MI Sxscore ≥19 were 4% and 8% at 30 days and 1 year, respectively. Differences in patient-oriented MACE were driven by a higher risk of death or reinfarction (9% in the $Sxscore_{high}$ group, 5% in the $Sxscore_{intermediate}$ group and 4% in the $Sxscore_{low}$ group, p < 0.001) as well as any revascularisation among patients in the highest risk tertile (9% in the $Sxscore_{high}$ group, 6% in the $Sxscore_{intermediate}$ group and 3% in the $Sxscore_{low}$ group, p = 0.002). Cardiac mortality was higher in the $Sxscore_{high}$ tertile compared to the $Sxscore_{low}$ tertile, HR 2.51 (1.03–6.10) p = 0.0423. The risk of repeat revascularisation was higher in the $Sxscore_{high}$, compared with the $Sxscore_{intermediate}$ and $Sxscore_{low}$ tertiles at 1 year ((9%) vs. 23 (6%) vs. 12 (3%) p = 0.002; $Sxscore_{high}$ vs. $Sxscore_{low}$ HR 3.24 (1.68–6.25), p = <0.001).

Definite and probable stent thromboses (STs) occurred early (within 30 days) in 26 patients and late (30 days to 1 year) in 8 patients. Early definite and probable STs were diagnosed in 13 (4%) of the $Sxscore_{high}$, 7 (2%) of the $Sxscore_{intermediate}$ and 6 (2%) of the $Sxscore_{low}$ (p = 0.081). Definite and probable STs at one year were recorded in 13 (4%) of the $Sxscore_{high}$, 9 (2%) of the $Sxscore_{intermediate}$ and 10 (3%) of the $Sxscore_{low}$ groups (p = 0.58).

3.2. Risk stratification according to TIMI score and MI Sxscore

A 10-point increase in the MI Sxscore was associated with an increased risk of patient- (HR = 1.83, 95% CI 1.43–2.32, p < 0.001) and device-oriented MACEs (HR of 1.48, 95% CI 1.10–1.98, p = 0.009).

Table 3
Clinical outcome at 30 days in the COMFORTABLE AMI trial according to Sxscore tertiles.

	SYNTAX score			Cox's regression				
	Low (0–10) N = 394	Intermediate (11–18) N = 374	High (19–52) N = 364	Intermediate vs. low		High vs. low		Overall
				HR (95% CI)	p value	HR (95% CI)	p value	p value
30 days follow-up								
Device-oriented MACE	6 (2%)	9 (2%)	16 (4%)	1.59 (0.57–4.48)	0.376	2.92 (1.14–7.46)	0.025	0.060
Patient-oriented MACE	6 (2%)	14 (4%)	25 (7%)	2.49 (0.96–6.49)	0.061	4.61 (1.89–11.24)	0.001	0.002
All cause death	3 (1%)	5 (1%)	9 (2%)	1.77 (0.42–7.42)	0.433	3.27 (0.89–12.09)	0.075	0.172
Cardiac death	3 (1%)	5 (1%)	8 (2%)	1.77 (0.42–7.42)	0.433	2.91 (0.77–10.96)	0.115	0.269
Reinfarction (any)	2 (1%)	4 (1%)	11 (3%)	2.14 (0.39–11.66)	0.381	6.04 (1.34–27.25)	0.019	0.027
Reinfarction in IRA	2 (1%)	3 (1%)	6 (2%)	1.60 (0.27–9.56)	0.608	3.27 (0.66–16.21)	0.147	0.288
Death or reinfarction (any)	5 (1%)	9 (2%)	20 (5%)	1.92 (0.64–5.73)	0.241	4.40 (1.65–11.71)	0.003	0.005
Revascularisation (any)	3 (1%)	9 (2%)	14 (4%)	3.20 (0.87–11.81)	0.081	5.15 (1.48–17.92)	0.010	0.033
Revascularisation in IRA, clinically indicated	3 (1%)	4 (1%)	9 (2%)	1.41 (0.32–6.32)	0.650	3.28 (0.89–12.11)	0.075	0.131
Stent thrombosis all	6 (2%)	7 (2%)	13 (4%)	1.24 (0.42–3.69)	0.697	2.37 (0.90–6.23)	0.081	0.152
Definite	3 (1%)	4 (1%)	7 (2%)	1.41 (0.32–6.32)	0.650	2.54 (0.66–9.84)	0.176	0.350
Definite/probable	6 (2%)	7 (2%)	13 (4%)	1.24 (0.42–3.69)	0.697	2.37 (0.90–6.23)	0.081	0.152
Probable	3 (1%)	3 (1%)	6 (2%)	1.07 (0.22–5.28)	0.938	2.18 (0.55–8.73)	0.269	0.429
Possible	0 (0%)	0 (0%)	0 (0%)					

Device-oriented MACE: cardiac death, repeat TLR clinically indicated, or MI in IRA; and patient oriented MACE: all cause death, reinfarction and revascularisation. IRA: infarct related artery. p value from Cox's regression Chi-square test.

Table 4
Clinical outcome 1 year in the COMFORTABLE AMI trial according to Sxscore tertiles.

	SYNTAX score			Cox's regression				
	Low (0–10) N = 394	Intermediate (11–18) N = 374	High (19–52) N = 364	Intermediate vs. low		High vs. low		Overall
				HR (95% CI)	p value	HR (95% CI)	p value	p value
1 year follow-up								
Device-oriented MACE	14 (4%)	22 (6%)	30 (8%)	1.68 (0.86–3.29)	0.128	2.38 (1.26–4.49)	0.007	0.026
Patient-oriented MACE	20 (5%)	33 (9%)	53 (15%)	1.79 (1.03–3.13)	0.039	3.05 (1.82–5.10)	<0.001	<0.001
All cause death	10 (3%)	11 (3%)	17 (5%)	1.17 (0.50–2.75)	0.719	1.87 (0.86–4.08)	0.117	0.235
Cardiac death	7 (2%)	10 (3%)	16 (4%)	1.52 (0.58–3.99)	0.396	2.51 (1.03–6.10)	0.042	0.107
Reinfarction (any)	8 (2%)	8 (2%)	14 (4%)	1.07 (0.40–2.85)	0.892	1.95 (0.82–4.66)	0.131	0.219
Reinfarction in IRA	6 (2%)	5 (1%)	6 (2%)	0.89 (0.27–2.91)	0.845	1.10 (0.35–3.41)	0.868	0.939
Death or reinfarction (any)	16 (4%)	18 (5%)	31 (9%)	1.20 (0.61–2.36)	0.588	2.17 (1.19–3.96)	0.012	0.021
Revascularisation (any)	12 (3%)	23 (6%)	34 (9%)	2.08 (1.04–4.18)	0.040	3.24 (1.68–6.25)	0.000	0.002
Revascularisation in IRA, clinically indicated	9 (2%)	13 (3%)	15 (4%)	1.54 (0.66–3.61)	0.318	1.85 (0.81–4.23)	0.144	0.340
Stent thrombosis all	12 (3%)	13 (3%)	21 (6%)	1.16 (0.53–2.53)	0.719	1.93 (0.95–3.93)	0.069	0.134
Definite	4 (1%)	4 (1%)	7 (2%)	1.06 (0.27–4.24)	0.933	1.91 (0.56–6.53)	0.301	0.488
Definite/probable	10 (3%)	9 (2%)	13 (4%)	0.96 (0.39–2.36)	0.926	1.43 (0.63–3.26)	0.398	0.577
Probable	6 (2%)	5 (1%)	6 (2%)	0.89 (0.27–2.91)	0.845	1.10 (0.35–3.40)	0.874	0.942
Possible	4 (1%)	5 (1%)	8 (2%)	1.33 (0.36–4.95)	0.671	2.21 (0.67–7.34)	0.195	0.389

Device-oriented MACE: cardiac death, repeat TLR clinically indicated, or MI in IRA; and patient oriented MACE: all cause death, reinfarction and revascularisation. IRA: infarct related artery. p value from Cox's regression Chi-square test.

Risk ratios of the individual TIMI risk score components were particularly predictive of death with little additional value in terms of the c-statistic by adding the MI Sxscore (without: 0.783; with 0.787). However, the model improved the prediction of patient- (0.623 to 0.692) and device-oriented outcomes (0.65 to 0.695) after addition of the MI Sxscore. The hazard ratios for the components and the c-statistics are shown in Table 5. The c-statistics of the score in observational studies is comparable (0.61) [6].

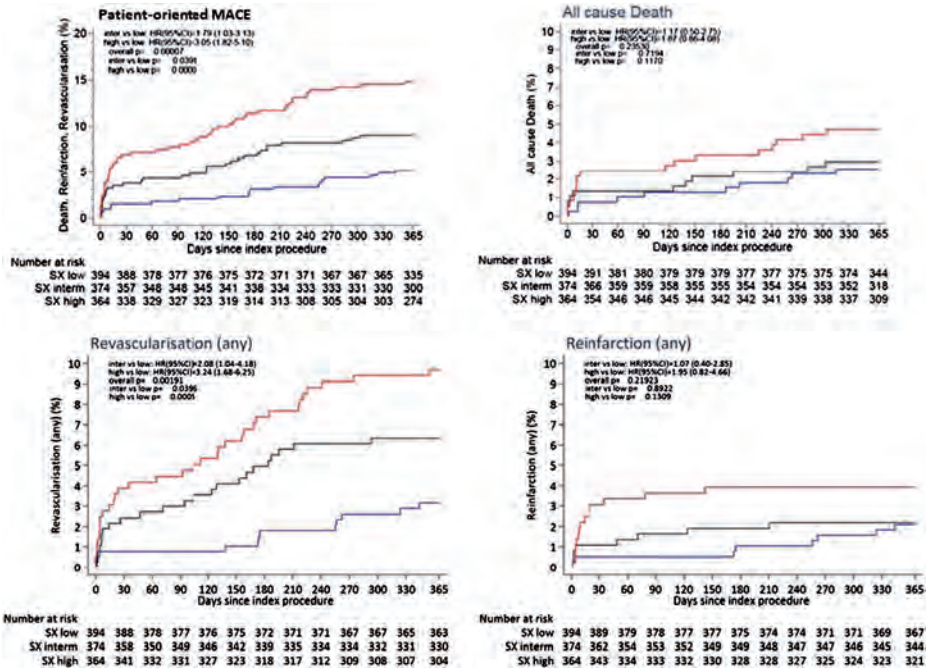


Fig. 2. Kaplan–Meier event curves and log rank tests for patients presenting with STEMI and categorised in tertiles of the MI Sxscore for 1 year patient-oriented major adverse cardiac events (MACEs) with its components separately shown; all-cause mortality, revascularisation and reinfarction. Red curve indicates MI $Sxscore_{high}$, black curve indicates $Sxscore_{intermediate}$ and blue curve indicates MI $Sxscore_{low}$.

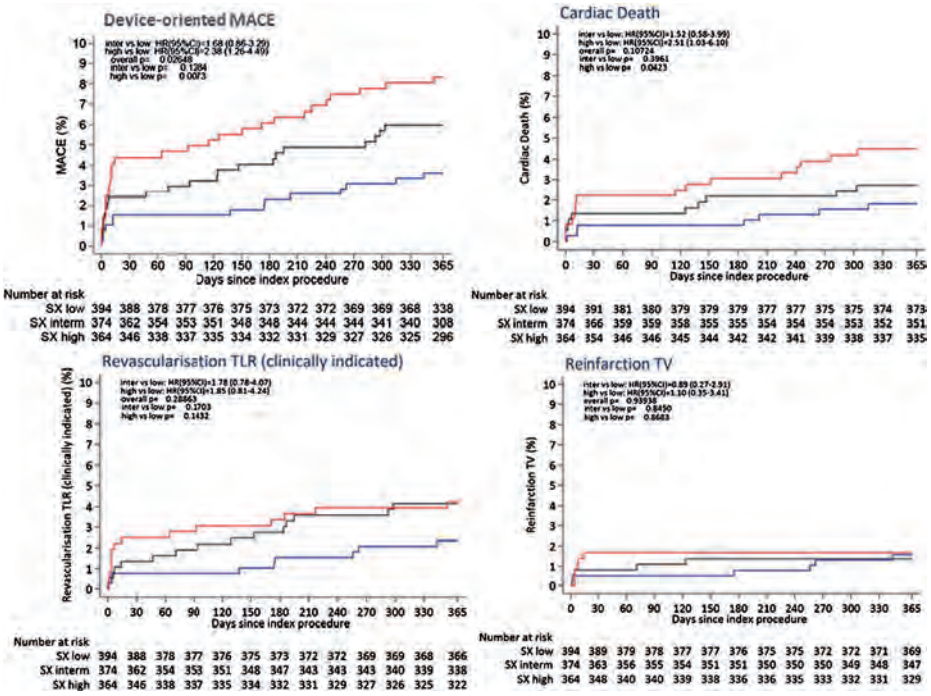


Fig. 3. Kaplan–Meier event curves and log rank tests for patients presenting with STEMI and categorised in tertiles of the MI Sxscore for 1 year device-oriented MACE with its components separately shown; cardiac death, target lesion revascularisation-TLR and target vessel reinfarction. Red curve indicates MI $Sxscore_{high}$, black curve indicates $Sxscore_{intermediate}$ and blue curve indicates MI $Sxscore_{low}$.

3.3. Performance of the MI Sxscore according to stent type

The MI Sxscore was available in 564 patients randomised to BMS and 568 patients randomised to biolimus-eluting stents. Patient-oriented MACE occurred more frequently with both stent types in the higher MI Sxscore tertiles (BMS $Sxscore_{low}$ vs. $Sxscore_{intermediate}$ vs. $Sxscore_{high}$ = 6% vs. 10% vs. 18%, p = 0.002; biolimus-eluting stents: 4% vs. 7% vs. 12% p = 0.029). Device-oriented MACE was more common among higher MI Sxscore tertiles treated with BMS ($Sxscore_{low}$ 4% vs. 7% vs. 13% p = 0.007) but not for DES ($Sxscore_{low}$ 3% vs. 5% vs. 4% p = 0.669). The difference in outcome between the two stent types was more evident among patients in the highest tertile compared to the lower tertiles (Fig. 4 and Supplementary Fig. 1; biolimus-eluting stents vs. BMS patient-oriented MACE: 12% vs. 18% (diff. 6%) in $Sxscore_{high}$; 6% vs. 4% (diff. 2%) in $Sxscore_{low}$; device oriented MACE: 13% vs. 4% (diff. 9%) in $Sxscore_{high}$; 4% vs. 3% (diff. 1%) in $Sxscore_{low}$).

4. Discussion

The MI Sxscore emerged as an important tool for risk stratification of STEMI patients treated by primary PCI in contemporary practise in the present study. Quantification of the extent and severity of coronary artery disease as well as the localisation and patency of culprit lesions and diseased segments other than the IRA proved useful to predict early and late major adverse cardiovascular events. Moreover, the risk assessment was complementary to the clinical TIMI risk score. Differences in clinical outcome, both in terms of patient- and device-oriented MACEs between stent types were most evident in the highest MI Sxscore groups.

Although the Sxscore was originally designed to evaluate revascularisation options among patients with multivessel disease, its application in all comer trials has allowed risk stratification across the entire range of patients with various clinical and angiographic characteristics [11,12]. A considerable proportion of patients included in such trials have stable coronary artery disease with a low risk for recurrent events. However, differences in outcome between stent types may be more easily elucidated among high-risk patients. Indeed, the MI Sxscore was found to provide additional value in risk stratification in the present all comer STEMI trial. Moreover, the present study confirms the discriminative value of the MI Sxscore among STEMI patients as previously suggested in observational studies [6,13].

The present analysis shows that patients with high MI Sxscore have an increased risk of mortality from cardiac causes. Patency of the IRA as well as multivessel disease are both known to impact on mortality among STEMI patients [14,15]. Both factors are integral parts of the MI Sxscore and likely contribute to its predictive value in terms of cardiac mortality. Since a low TIMI flow adds to the score, patients in the higher

Table 5
Hazard ratios for mortality and patient and device-oriented MACE at 1 year for the TIMI risk variables, Sxscore and the respective c-statistics for prediction of endpoints with and without the MI Sxscore.

	All-cause death				Patient-oriented MACE				Device-oriented MACE			
	Model 1 without SX		Model 1 with SX		Model 2 without SX		Model 2 with SX		Model without SX		Model with SX	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Parameters												
Intercept	0.004 (0.002–0.011)	<0.001	0.003 (0.001–0.009)	<0.001	0.027 (0.015–0.048)	<0.001	0.017 (0.008–0.034)	<0.001	0.048 (0.031–0.076)	<0.001	0.022 (0.012–0.039)	<0.001
TIMI STEMI risk score parameters												
Age 65–74 years	1.335 (0.545–3.271)	0.528	1.281 (0.520–3.153)	0.590	1.031 (0.528–2.010)	0.929	0.973 (0.497–1.905)	0.937	1.298 (0.783–2.151)	0.312	1.188 (0.711–1.983)	0.511
Age >74 years	3.843 (1.682–8.781)	0.001	3.580 (1.556–8.236)	0.003	2.677 (1.396–5.132)	0.003	2.427 (1.255–4.693)	0.008	2.326 (1.346–4.018)	0.002	2.008 (1.145–3.522)	0.015
History of diabetes, hypertension or heart failure	2.494 (1.125–5.531)	0.024	2.402 (1.081–5.338)	0.031	1.508 (0.884–2.572)	0.132	1.448 (0.846–2.479)	0.177	1.383 (0.904–2.115)	0.135	1.312 (0.852–2.020)	0.218
Blood pressure <100 mm Hg	1.784 (0.627–5.077)	0.278	1.822 (0.637–5.212)	0.263	1.939 (0.905–4.155)	0.089	1.966 (0.911–4.242)	0.085	1.621 (0.837–3.139)	0.152	1.688 (0.860–3.310)	0.128
Heart rate >100 pulses	2.603 (0.970–6.988)	0.058	2.474 (0.907–6.753)	0.077	1.116 (0.417–2.984)	0.827	1.036 (0.378–2.840)	0.945	1.163 (0.528–2.559)	0.708	1.092 (0.482–2.472)	0.833
Killip II, III or IV	3.437 (1.410–8.374)	0.007	3.023 (1.210–7.549)	0.018	2.535 (1.201–5.352)	0.015	2.174 (1.012–4.669)	0.046	2.030 (1.054–3.911)	0.034	1.610 (0.817–3.175)	0.169
Body weight <67 kg	1.264 (0.543–2.939)	0.587	1.325 (0.570–3.082)	0.513	0.725 (0.338–1.554)	0.409	0.756 (0.354–1.617)	0.472	0.948 (0.534–1.681)	0.854	0.987 (0.554–1.757)	0.964
Anterior, anteroseptal or anterolateral MI	2.006 (1.015–3.964)	0.045	1.792 (0.890–3.611)	0.103	1.572 (0.942–2.623)	0.084	1.327 (0.782–2.252)	0.295	1.355 (0.896–2.050)	0.150	1.035 (0.672–1.596)	0.875
Time to Treatment >4 h	2.208 (1.022–4.771)	0.044	2.154 (0.993–4.674)	0.052	1.201 (0.711–2.030)	0.494	1.152 (0.678–1.957)	0.601	1.345 (0.883–2.046)	0.167	1.269 (0.827–1.946)	0.275
SYNTAX score (per 10 points)			1.309 (0.889–1.928)	0.172			1.477 (1.100–1.983)	0.009			1.827 (1.436–2.323)	<0.001
Concordance statistic C	0.783		0.787		0.653		0.695		0.623		0.692	

Device-oriented MACE: cardiac death, repeat TLR clinically indicated, or MI in IRA; and patient oriented MACE: all cause death, reinfarction, revascularisation odds ratios from logistic regression with C = Harrell's c concordance statistic. Age <65 years is the reference category, N = 1132 patients each model.

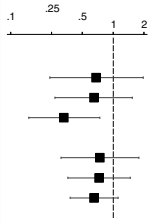
tertiles of the MI Sxscore are more likely to present with an occluded infarct related artery, an angiographic characteristic known to be associated with larger infarct sizes, and poorer prognosis. The higher prevalence of cardiovascular events among STEMI patients with multivessel disease is most likely multifactorial. First, the number of diseased vessels is often a reflection of the extent and severity of coronary atherosclerosis. Patients with multivessel disease therefore bear a higher risk of future events related to coronary artery disease progression or related to incomplete revascularisation, which is more prevalent in patients with higher baseline SYNTAX score, as previously shown in acute coronary syndrome patients [16]. Incomplete revascularisation is known to impact outcome in patients with residual coronary artery disease. Timely treatment of residual non-culprit coronary artery disease (within 90 days of the primary PCI) has therefore been advocated by the COMFORTABLE AMI study group. Since by definition high MI Sxscore patients often have multivessel disease and therefore residual disease, the risk of cardiovascular events related to non-culprit vessel disease certainly has an impact on the patient related outcome and therefore is an important determinant of the prognostic power of the MI Sxscore. Second, the increased procedural complexity reflected in a higher number of stents, a longer stent length and a higher rate of bifurcation treatment observed in the higher SXscore tertiles of this trial expose patients to an increased risk for re-stenosis and stent thrombosis [17,18]. Multivessel disease and high MI Sxscores were associated with a higher prevalence of the 'no-reflow' phenomenon, which reflects impaired myocardial reperfusion with its attendant effects on cardiovascular outcome [19]. In fact, in the present study, poor reperfusion as measured by TIMI flow at the end of the procedure and myocardial blush grade was more common in the higher Sxscore tertiles. The larger infarct size as determined by cardiac biomarkers in patients with the higher MI Sxscores observed in the current analysis lends support to the pathophysiological role of multivessel disease, IRA patency and myocardial reperfusion and provides insights on their link to clinical outcome.

The trend for a higher risk of early stent thrombosis among STEMI patients with high Sxscores observed in the present study corroborates the findings of a pooled analysis of 7 studies with 6496 patients [20]. In a subanalysis of 2093 acute coronary syndrome (ACS) patients in this study, higher rates of ST were observed in high Sxscore groups. The risk of ST among ACS patients treated with drug-eluting stents has been consistently higher than that in patients with stable coronary artery disease [17]. A large thrombus burden, frequently associated with impaired TIMI flow which is more prevalent in high Sxscore patients, plays an important role in the pathogenesis of stent thrombosis [21]. In addition, patients with high Sxscores often undergo treatment of bifurcations and implantation of longer stents, both risk factors for stent thrombosis. Moreover, the individual response to antiplatelet treatment is frequently impaired among diabetic patients, those with high BMI, and the elderly, characteristics predominantly present in patients in the highest Sxscores [22,23]. Interestingly, we observed a trend towards a higher rate of ST in the early phase after primary PCI in the higher Sxscore tertiles. Timely identification of high risk patients may allow for implementation of preventive measures such as the use of GPIIb/IIIa inhibitors and thrombectomy devices.

The MI Sxscore applied to STEMI patients provides incremental predictive value over clinical variables integrated in the TIMI score as previously shown in registry data [6]. Predictive clinical risk variables and their application in risk scores initially focused on early survival after STEMI [1]. The availability of angiographic characteristics in the primary PCI era provided additional prognostic information including TIMI flow in the infarct related artery and the presence of multivessel disease as factors associated with increased mortality. The MI Sxscore provides a similar predictive value in terms of 1-year mortality as the traditional TIMI risk score (0.783 to 0.787). The MI Sxscore incorporates patency of the infarct related artery and the myocardial area at risk. Compared with patients with low MI Sxscores, patients in the highest tertile have almost double the incidence of anterior myocardial infarction

SYNTAX Subgroup Analyses of the 1-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive Either the Biolimus-Eluting Stent or the Bare-Metal Stent

	Biolimus-Eluting Stent N = 568		Bare-Metal Stent N = 564		HR (95% CI)	p-value
	n	events (%)	n	events (%)		
Device-oriented MACE						
SYNTAX 0-10	205	6 (2.9)	189	8 (4.4)	0.68 (0.24-1.97)	0,479
SYNTAX 11-18	175	8 (4.7)	199	14 (7.2)	0.65 (0.27-1.54)	0,326
SYNTAX 19-52	188	8 (4.3)	176	22 (12.6)	0.33 (0.15-0.74)	0,007
Patient-oriented MACE						
SYNTAX 0-10	205	9 (4.4)	189	11 (6.0)	0.74 (0.31-1.79)	0,506
SYNTAX 11-18	175	13 (7.6)	199	20 (10.2)	0.73 (0.36-1.47)	0,380
SYNTAX 19-52	188	22 (11.9)	176	31 (17.8)	0.65 (0.38-1.12)	0,123



Device- oriented MACE: cardiac death, repeat TLR clinically indicated, or MI in IRA
Patient-oriented MACE: death, reinfarction or revascularisation
IRA: infarct related artery
p-value from Cox's Regression chi-square test

Fig. 4. SYNTAX subgroup analyses of the 1-year rates of major adverse cardiac events among patients randomised to receive either the biolimus-eluting stent or the bare-metal stent.

and impaired TIMI flow of the IRA, which result in a larger infarct size and two-fold increased mortality during the first year. The combination of the MI Sxscore and the TIMI risk score afforded improved discrimination of patient- and device-oriented MACEs as compared with either score alone. Moreover, the combined score was superior in the prediction of cardiac death and myocardial infarction and repeat revascularisation procedures. The addition of angiographic information to standard clinical variables is easily obtainable in STEMI patients undergoing primary PCI and offers improved prediction of adverse events and prognosis. The use of BMS in STEMI has resulted in a higher incidence of device-oriented MACE when compared to DES [8]. Stratification of MI Sxscores according to implanted stent platform supports the notion that differences in clinical outcomes between stent types are more pronounced in the highest MI Sxscore tertile. The observation in differentiation of outcome between stent types is consistent with that of previous Sxscore analysis in the LEADERS and SIRTAX trials [12,24]. Thrombogenicity of the stent coating and suppression of neointima by drug elution may be particularly important in complex lesions with high thrombus load and may explain the lower ST event rates observed in BES implanted in high-risk patients. Similarly, the risk of restenosis and therefore repeat revascularisation procedures is more pronounced in patients with higher MI Sxscores.

4.1. Study limitations

Several limitations need to be considered in the interpretation of the present study. The present analysis focused on patient- and device-oriented composite outcomes. However, findings on individual endpoints including mortality and stent thrombosis have to be interpreted with caution due to the limited number of patients and events and should therefore be considered hypothesis generating. The evaluation of the MI Sxscore was performed by experienced assessors, and it is uncertain whether the same robustness can be maintained in routine clinical practise. We have not assessed the residual SYNTAX score following protocol mandated complete revascularisation within 3 months after primary PCI. Therefore we cannot conclude on the impact of incomplete revascularisation following treatment of ST-elevation patients. In the current study the relation of the MI Sxscore and microvascular reperfusion was drawn from angiographic data of myocardial blush grade and TIMI flow. The relation of the score with a non-angiographic and therefore more independent means of measuring microvascular reperfusion such as ST segment resolution or gadolinium enhanced magnetic resonance imaging-derived microvascular obstruction was not available but may be further evaluated and confirmed in future research.

5. Conclusions

The MI Sxscore is a validated risk stratification tool in the assessment of adverse cardiovascular outcomes among STEMI patients undergoing primary PCI throughout one year. It provides added prognostic value beyond clinical risk scores such as the TIMI risk score and shows the highest discrimination between stent types in the highest MI Sxscore.

Disclosures

Clinical Trials Unit (CTU Bern), which is part of the University of Bern, Bern, Switzerland, has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in the design, conduct, or analysis of clinical studies funded by Abbott Vascular, Ablynx, Amgen, AstraZeneca, Biosensors, Biotronic, Boehringer Ingelheim, Eisai, Ei Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novo Nordisk, Padma, Roche, Schering-Plough, St. Jude Medical, and Swiss Cardio Technologies (33CM30–124112 and 310030–118353).

Dr. Baumbach reported being on advisory boards and receiving consultancy fees from Boston Scientific, Medicines Company, and Abbott Vascular; and receiving payment for lectures from Medicines Company and Japan Stent Inc. Dr. Tüller reported receiving travel expenses from Biotronik, Biosensors, Terumo, and Medtronic. Dr. von Birgelen reported board memberships and receiving lecture fees from Abbott Vascular, Medtronic, and Boston Scientific; receiving consultancy fees from Medtronic; unpaid consultancies from Abbott Vascular, Boston Scientific, Biosensors, Biotronik, and Cordis; receiving grants from Abbott Vascular, Boston Scientific, Biosensors, Biotronik, Cordis, Medtronic, and St. Jude Medical; payment for lectures from Abbott Vascular, Boston Scientific, Medtronic, and MSD; and receiving payment for development of educational presentations from Cordis. Dr. Roffi reported receiving grants from Boston Scientific, Abbott Vascular, Medtronic, and Biosensors; and payment for lectures from Lilly-Daiichy Sankyo. Dr. Lüscher reported receiving research grants for the institution from Abbott, Biosensors, Biotronik, Boston Scientific, and Medtronic, and consultant payments from AstraZeneca, Boehringer Ingelheim, Bayer, Merck, and Pfizer. Dr. Meier reported receiving research contracts for

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.05.029.

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5.9

Residual atherothrombotic material after stenting in acute myocardial infarction--an optical coherence tomographic evaluation.

Magro M, Regar E, Gutiérrez-Chico JL, Garcia-Garcia H, Simsek C, Schultz C, Zijlstra F, Serruys PW, van Geuns RJ.

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Residual atherothrombotic material after stenting in acute myocardial infarction — An optical coherence tomographic evaluation

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ABSTRACT

Background: Thrombus aspiration (TA) in patients with ST segment elevation myocardial infarction (STEMI) results in a better myocardial perfusion. Optical coherence tomography (OCT) after stenting in STEMI, however, often reveals residual atherothrombotic material. We assessed the feasibility of quantification of residual atherothrombotic burden and its relation to indices of myocardial perfusion. The effect of TA on residual in-stent atherothrombotic burden (ATB) is explored.

Methods and results: Forty patients with STEMI within 12 h of symptom onset, underwent OCT after stent implantation. No complication related to the invasive imaging was detected and all cases had good image quality. All 40 cases revealed ATB (median, range; 2.85, 0.08–8.84) despite an optimal angiographic result. Patients were divided into two groups according to the ATB: $\geq 4 = ATB_{high}$ ($n = 15$) and $<4 = ATB_{low}$ ($n = 25$). Patients with ATB_{low} more often obtained a myocardial blush grade (MBG) of 2/3: 24 (96%) vs. 11 (73%), $p = 0.04$ and a $\geq 50\%$ ST segment resolution 24 (96%) vs. 8 (53%) $p = 0.02$. Incomplete stent apposition is more often detected with ATB_{low}: 1.97 (0.62–4.73) vs. 0.33 (0.04–0.92), $p = 0.002$. TA was performed in 20 (50%) patients. ATB was numerically lower in patients with TA: 2.37 (1.70–5.10) vs. 3.40 (1.45–4.96), $p = 0.67$. Logistic regression identified ATB as predictor of ST resolution failure (OR: 2.5 (95% confidence interval: 1.27–4.98), p value = 0.008).

Conclusions: OCT can be safely performed in patients presenting for primary PCI and allows quantification of residual atherothrombotic material, the amount of which is associated with worse myocardial perfusion.

1. Introduction

A high thrombus load as detected by coronary angiography during primary percutaneous coronary intervention is an important determinant of myocardial reperfusion and major adverse cardiac events [1,2]. Manual thrombus aspiration improves myocardial perfusion and may decrease cardiac death in STEMI patients [3,4]. This effect is at least in part driven by a reduction in thrombus burden which in turn improves distal blood flow, reduces distal embolisation and thereby improves microvascular perfusion [5]. The latter has a direct influence on the final infarct size and together have a significant impact on the short and long term clinical outcome [6].

Optical coherence tomography (OCT) can detect atherothrombotic material in the culprit lesion better than any other imaging modality [7]. Due to its high spatial resolution, OCT can also quantify very small intravascular structures especially those close to the surface of the endothelium. Residual intra-stent material representing atherothrombotic material has been observed with OCT particularly in the setting of acute coronary syndromes [8]. The significance of the amount of residual atherothrombotic material has not been established. Moreover whether primary percutaneous coronary intervention with manual thrombus aspiration effects the in-stent residual atherothrombotic burden is yet unknown. The aims of this prospective exploratory study were firstly to assess the feasibility and reproducibility of measurement of residual atherothrombotic burden after stenting. Secondly, the implications of a high versus a low residual atherothrombotic burden as measured by OCT on indices of microvascular perfusion were explored. Thirdly, we assessed if primary percutaneous coronary intervention (PPCI) with thrombus aspiration (TA) results in a lower atherothrombotic burden as compared to PPCI without TA.

2. Methods

2.1. Study population

Patients referred to our hospital within 12 h of an episode of continuous chest pain lasting > 30 min and having a 12 lead electrocardiogram (ECG) with ST-segment elevation ≥ 0.1 mV in 2 or more contiguous leads and an angiographically identifiable culprit lesion in a native coronary artery were eligible for enrolment in this study. Patients who were haemodynamically unstable even after corrective measures, as well as patients with a previous stent implantation in the culprit coronary artery were excluded. Also patients in whom successful wiring of the culprit artery and TIMI ≥ 1 flow allowed angiographic visualisation of a very high thrombus load were excluded. Furthermore

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patients in whom thrombus aspiration was mandatory according to the treating interventional cardiologist were excluded.

2.2. Procedure

Intravenous heparin (100 U/kg), aspirin (300 mg), clopidogrel (600 mg) and oxygen (5 l/min via mask or nasal pronges) were systematically administered immediately on diagnosis at the first point of medical contact which is pre-hospital in the majority of cases. Nitrates and analgesics (diamorphine) were instituted when necessary. Cardiac catheterisation was performed via the femoral or radial approach using a 6-F sheath and appropriate catheters. After contrast injection and angiographic filming of both left and right coronary systems, the culprit artery was identified by angiographic signs including absent or reduced thrombolysis in myocardial infarction (TIMI) flow, evidence of thrombus, and signs of myocardial infarction in the corresponding territory by ECG and/or transthoracic echocardiography. Engagement of the ostium of the artery was followed by intracoronary bolus of nitrate (2 mg) and an angiogram. After successful wiring of the vessel with advancement of the wire well beyond the culprit site a second cine angiography was taken. This allowed assessment and reclassification of thrombus grade in patients with TIMI 0 on the first film. At this stage, the interventional cardiologist chose to treat the patient with or without manual thrombus aspiration. In our institution, TA is employed in about 70% of all PPCIs and in about 50% of those with low-intermediate angiographic thrombus grades. By exclusion of high thrombus grades from the study we projected equal distribution of TA and non-TA use in the study cohort.

2.3. Manual thrombus aspiration

A thrombectomy catheter (DIVER, Invatec-Medtronic) was advanced over the wire and the radio-opaque marker was used to position the tip just proximal to the point of occlusion or lesion. A negative pressure was then applied by means of a 30 ml syringe. The catheter tip was slowly advanced across the lesion while maintaining aspiration. Slow retraction of the catheter tip to a site proximal to the culprit lesion allowed re-cross. This manoeuvre was repeated 2–4 times after which a control angiography was performed. In case of residual thrombotic appearance on angiography, further aspiration runs were performed.

Small balloons (<1.5 mm diameter) were used where appropriate in patients in the no thrombectomy arm with the aim of improving in TIMI flow and thereby allowing assessment of the culprit lesion in patients presenting with TIMI 0/1. Predilatation with a ballon >1.5 mm was strongly discouraged in favour of direct stenting in both treatment arms.

2.4. Optical coherence tomography image acquisition

OCT acquisition was performed with the C7-XR imaging system (St. Jude/LightLab Imaging, Inc, Westford, MA) after angiographic optimal stent implantation and once the treating cardiologist deemed the interventional treatment complete. The image catheter (Dragonfly™, St. Jude/LightLab Imaging, Inc, Westford, MA) was advanced and positioned distal to the stented segment. A continuous flush of iso-osmolar contrast through the guiding catheter (Iodixanol 370, Visipaque™, GE Health Care, Ireland) at 3–4 ml/s was used for blood clearance while an automated OCT pullback was performed at 20 mm/s. Post-dilatation, further thrombus aspiration and any repeat intervention driven primarily by the OCT findings during this pullback were permitted but left to the discretion of the operator and were not included in the main data analysis.

2.5. Angiographic analysis

Offline angiographic analysis including quantitative coronary angiographic (QCA) measurements was performed using CAAS 5.5 (Pie Medical, Maastricht, the Netherlands). Thrombus grade (TG) was determined before and after wiring. Thrombus grade of 0 was defined as no angiographic sign of thrombus; 1 — reduced contrast density, haziness, irregular lesion contour suggestive but not diagnostic of thrombus; 2 — definite thrombus with greatest dimensions ≤1/2 the vessel diameter; 3 — definite thrombus with greatest linear dimension >1/2 but <2 vessel diameters; 4 — definite thrombus with the largest dimension ≥2 vessel diameter; 5 — total occlusion [9]. Reclassification after wiring allowed changes in grading especially for those in which TIMI flow changes from 0 to 1 or higher [2]. Thrombolysis in myocardial (TIMI) flow and myocardial blush were assessed as previously reported [10]. No reflow was defined as reduced antegrade flow to TIMI 0/1 after achievement of TIMI 2/3 flow, in the absence of occlusion at the treatment site or evidence of distal embolisation. Slow flow was defined as a decrease in antegrade flow to TIMI 1/2 after stent implantation when compared to optimal TIMI 2/3 flow pre-stent implantation. Distal occlusion was defined as a filling defect distal from the culprit site causing an abrupt cut-off of the distal vessel or branch. Myocardial blush grade (MBG) was measured as previously described [11].

Acute gain was calculated as a change in minimal luminal diameter in the stent area. For all patients including those with TIMI 0 at presentation, the film before balloon/stent inflation was used for pre-procedural minimal luminal diameter (MLD), allowing a more realistic measurement of the actual acute gain. The rest of the QCA parameters were measured as previously described [12].

2.6. ST segment resolution and peak cardiac enzymes

ST segment resolution was defined as a ≥50% decrease in the ST segment elevation between the pre-procedural 12-lead ECG showing the highest elevation and the ST segment elevation on a 12 lead ECG taken 1 h after the procedure. Blood samples for cardiac enzymes (creatinine kinase) were taken regularly every 6 h. The peak enzyme values were included in the database.

2.7. OCT safety and feasibility measures

Safety of OCT on imaging related complications such as vasospasm, dissection, embolisation, arrhythmia, and other major adverse cardiovascular events that were clearly related to the imaging procedure or any other event was recorded [13]. Image quality and appropriateness for planned analysis was also assessed.

2.8. OCT analysis

Off-line analysis was performed with the Light Lab software on a dedicated workstation in a core lab setting by an experienced analyst, blinded to treatment assignment, and angiographic or clinical outcome. After correction of the Z-Offset, the stented segment including the 5 mm proximal and distal peri-stent regions was identified and bookmarked. This allowed systematic analysis in 1 mm intervals. The longitudinal view was used to mark and measure the length of the stent (region of interest — ROI and the thrombotic region of interest — TROI). The latter was defined by the distance between the most distal and the most proximal cross-sectional frame that showed intraluminal material suggestive of thrombus as described by Kubo et al. [14]. The lumen area (LA) was obtained by automated edge-detection algorithm and additional manual corrections, when necessary. The stent area (SA) was obtained by a multiple point detection function which linked the points set in the middle of the endoluminal border of stent struts. Intraluminal material which was not clearly attached at any point to the endothelial wall in that frame was measured by multiple point trace function and labelled as free thrombus (FTA). The area between malapposed stent struts and the vessel wall was measured and labelled as incomplete stent apposition area (ISA). The atherothrombotic area (ATA) was calculated by subtracting the LA from the SA and adding FTA while taking into account ISA:

$$ATA = SA–LA + FTA + ISA.$$

The atherothrombotic volume (ATV) was calculated by multiplying the mean ATA by the TROI length:

$$ATV = \text{mean ATA} \times TROI.$$

The atherothrombotic burden (ATB) was then calculated as a percentage of stent volume (SA multiplied by ROI) and expressed as a percentage:

$$ATB = ATV/SV \times 100.$$

The derivation of this parameter is further illustrated in Fig. 1.

2.9. Reproducibility of the OCT measurements

The first 11 pullbacks were analysed by a second experienced observer to determine interobserver variability of atherothrombotic burden measurement. These same pullbacks were analysed by the main observer >4 weeks apart to obtain intraobserver variability of the measurements.

2.10. Clinical follow-up

Hospitals to which the patients were discharged after the PPCI were contacted for information on relevant clinical events during the hospitalisation following the index event. Patients had clinical visits or were contacted by phone or mail at 6 months and were specifically asked for symptoms or re-admissions following their index events. Hospital records, general practitioners and peripheral hospitals were contacted for details in case of an event which was then adjudicated by 2 cardiologists with criteria as previously described [15].

2.11. Statistical analysis

Continuous variables are expressed as means (SD) or median and interquartile range. Categorical variables are expressed as percentages. The distribution of ATB in the whole cohort was assessed on a frequency chart. The distribution curve showed a positive skew, with the bulk of the values (and therefore the median) lying to the left of the mean residual ATB value. Since the measurement of interest was ATB, patients were divided into two cohorts; those with ATB below the mean i.e. <4% or ATB_{low} and those with ATB above the mean i.e. ≥4% or ATB_{high}. Comparisons between these groups were performed with chi-squared test for categorical variables whereas the Student *t* test or Mann Whitney test was used to compare continuous variables. Multiple logistic regression analysis was performed to assess the independent predictors of failure of ST segment resolution as a measure of myocardial/microvascular perfusion. In a first step, univariate analysis was used to assess predictors of failure of ST resolution. These included

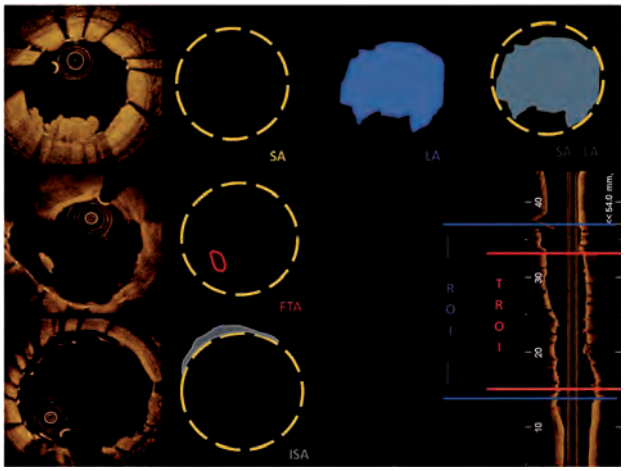


Fig. 1. Measurement of residual in-stent atherothrombotic burden by optical coherence tomography. Optical coherence tomography (OCT) cross sections taken from patients immediately after stent implantation during primary percutaneous coronary intervention. Intraluminal material extending toward the lumen beyond the defined stent area is considered as thrombus or atherothrombotic material for the purposes of this study. By subtracting the lumen area (LA) from the stent area (SA) this part is obtained. Free thrombus area (FTA) is added to (SA–LA) while areas of incomplete stent apposition (ISA) are added to obtain the mean atherothrombotic area for any given OCT frame. The length over which thrombus is detected in the longitudinal view that is the atherothrombotic region of interest (TROI) is used to calculate a mean atherothrombotic volume. This is then corrected for stent volume (ROI × SA) to obtain the atherothrombotic burden which is expressed as a percentage (see text).

age, shock, pain to balloon time multivessel disease, anterior myocardial infarction, left anterior descending, TIMI 0 presenting, and angiographic thrombus grade and ATB. Parameters with value of <0.1 were then entered into a multivariate model to assess their independent association with failure of ST resolution.

For analysis of the effect of thrombus aspiration on atherothrombotic burden, patients were divided into two groups according to intention to treat. The exploratory nature of the study precluded an up-front formal power calculation of the number of patients needed to include in the study to detect difference in atherothrombotic burden between the two groups. Baseline clinical, procedural and OCT measures including ATB were compared using Student *t* test or chi square test as appropriate.

The interobserver and intraobserver reproducibility of the residual atherothrombotic burden was calculated by estimating the absolute and relative differences between measurements. The relative difference was defined as the absolute difference divided by the average. The data including the limits of agreement (calculated as the mean difference ± 2SD) are depicted in Bland–Altman plots.

3. Results

OCT pullback was feasible in all patients after stent implantation. There were 6 cases where embolisation of atherothrombotic material was observed however in all cases this was present before insertion of the OCT imaging catheter. There was no major adverse event that could be attributed to the OCT imaging procedure.

All the OCT images were of good quality for analysis. Residual atherothrombotic burden could be measured in all 40 cases (median, range; 2.85%, 0.08–8.84) by OCT as opposed to none on angiography. There were no significant differences between patients with an ATB_{high} (n = 15) and ATB_{low} (n = 25) in the baseline clinical characteristics (Table 1). A high ATB was more likely to occur in a vessel with larger reference diameter as measured pre-intervention by quantitative coronary angiography: 3.13 ± 0.65 mm vs. 2.64 ± 0.50 mm, p = 0.02. Patients with an ATB_{high} more often developed no reflow: 3 (20%) vs. 0 (0%), p = 0.02; embolisation: 5 (33%) vs. 1 (4%), p = 0.008 and distal occlusion: 4 (27%) vs. 1 (4%), p = 0.03. Those with an ATB_{low} more often obtained a MBG of 3: 24 (96%) vs. 11 (73%), p = 0.04 and a ≥ 50% ST segment resolution 24 (96%) vs. 8 (53%) p = 0.02. (see Figs. 2 and 3). Incomplete stent apposition as measured by incomplete stent apposition volume (ISV) was higher in patients with ATB_{low}: 1.97 (0.62–4.73) vs. 0.33 (0.04–0.92), p = 0.002. No association with respect to infarct size as measured by peak creatinine kinase (CK) was found.

Multiple logistic regression was performed to determine the independent predictors of failure to achieve complete ST resolution. In a multivariate model including angiographic thrombus grade, residual atherothrombotic burden, and thrombectomy, the only independent predictor of failure of ST resolution was residual atherothrombotic burden with an odds ratio of 2.51 (95% confidence interval: 1.27–4.98), p value = 0.008. Furthermore, addition of other baseline parameters in the multivariate model did not significantly change the odds ratio for ATB.

3.1. Thrombus aspiration vs. no aspiration

Baseline clinical characteristics were similar in both treatment groups (Table 2). Manual thrombus aspiration (TA) was more often performed in patients with TIMI 3 flow: 11 (55%) vs. 3 (15%) p = 0.02, however there was no difference in angiographic thrombus (TG) graded after wiring of the culprit coronary artery TG 1–3, 19 (95%) vs. 18 (90%) p = 1.0 (Table 3).

In the TA group, patients had an average of 2 aspiration runs. Macroscopic atherothrombotic material on the collection sieve was observed in only 25% of those undergoing this adjunctive interventional therapy. Procedure duration was significantly longer (50 min vs. 39 min, p = 0.02) in the thrombus aspiration group. Other procedural characteristics however were not different between the two treatment arms as shown in Table 4. Everolimus eluting stents (XIENCE V, Abbott Vascular, Santa Clara, CA) were used in the majority of patients. The bare metal stents implanted had the same stent design as the drug-eluting stents (Multilink Vision, Abbott Vascular, Santa Clara, CA). Stent overlap was deemed appropriate in 23% while postdilatation (non-OCT

Table 1
Baseline clinical characteristics, angiographic and procedural characteristics in patients with low and high atherothrombotic burden.

Characteristic	OCT ATB<4 n=25	OCT ATB≥4 n=15	p value
Baseline characteristics			
Age, years	62±12	65±8	0.34
Male	23 (92)	12 (80)	0.27
Diabetes	3 (12)	2 (13)	0.80
Hypertension	6 (25)	8 (53)	0.06
Hypercholesterolaemia	10 (40)	5 (33)	0.67
Current Smoker	12 (48)	5 (33)	0.36
Family History of CAD	9 (36)	7 (47)	0.51
Clinical presentation			
Ischaemic time, min	312±133	318±271	0.85
Pulse, bpm	74±16	72±19	0.39
Blood pressure, mm Hg			
Systolic	125±25	132±36	0.85
Diastolic	78±11	75±19	0.59
Cardiogenic shock	1 (4)	0 (0)	0.43
Killip class 1	24 (96)	15 (100)	0.43
Infarct related artery			
LAD	10 (40)	6 (40)	1.0
LCx	3 (12)	2 (13)	0.90
RCA	12 (48)	7 (47)	0.94
TIMI flow grade			
0	13 (52)	6 (40)	0.53
1	2 (8)	0 (0)	0.52
2	3 (12)	2 (13)	0.90
3	7 (28)	7 (47)	0.31
Thrombus grade after wiring			
1	5 (20)	1 (7)	0.26
2	6 (25)	8 (53)	0.06
3	11 (44)	5 (33)	0.51
4	2 (8)	1 (7)	0.88
5	1 (4)	0 (0)	0.43
Multivessel disease	14 (56)	9 (60)	0.81
Procedural characteristics			
Thrombus Aspiration	13 (52)	7 (47)	0.74
Macroscopic thrombus visible on sieve	4 (16)	1 (7)	0.47
Use of small balloon pre-stenting	4 (16)	4 (27)	0.42
Stent implanted			0.33
EES[a]	19 (36)	9 (60)	
BMS[a]	4 (16)	5 (33)	
GP IIb/IIIa inhibitors	9 (36)	12 (80)	0.008

Data are expressed as means (standard deviation) and number (percentages). OCT TB = in-stent residual atherothrombotic burden, LAD = left anterior descending coronary artery, LCx = left circumflex coronary artery, RCA = right coronary artery. TIMI = thrombolysis in myocardial infarction, EES = everolimus eluting stent, BMS bare metal stent, GP glycoprotein.
[a] Same multi-link design.

driven) was performed in 48%. Glycoprotein IIb/IIIa inhibitors were given in 53% of patients.

OCT parameters measured in both groups are shown in Table 5. The stented length (ROI, mm) was longer for patients with TA 26 (20–32), vs. 18 (15–25) p=0.04. OCT measurements of atherothrombotic material were numerically lower in the TA group however none reached statistical significance. Thus the TROI (mm) that is the length over which the atherothrombotic material was measured was: 20 (11–26) vs. 12 (10–25), p=0.21; residual atherothrombotic burden was also 30% lower in the TA group, however no statistical significance was reached; TB: 2.37 (1.70–5.10) vs. 3.40 (1.45–4.96), p=0.67; (see Fig. 4). As consequence the minimal flow area as a ratio of mean stent area was numerically higher for TA patients (0.75±0.10 vs. 0.77±0.15 p=0.64) indicating a possibly lower degree of narrowing in the stented segment. Incomplete stent strut apposition was not different between the two groups. There was no difference in terms of angiographic complications including slow flow, no-reflow, embolisation, or distal occlusion. The same number of patients with and without TA achieved optimal MBG 2/3 (18,

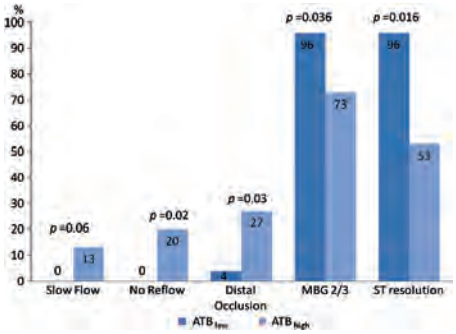


Fig. 2. Microvascular perfusion in patients with high or low residual in-stent atherothrombotic material. In-stent residual atherothrombotic burden was categorised into low that is <4% (ATB_{low}) and high, that is ≥4% (ATB_{high}) according to frequency distribution. The difference in the occurrence of angiographically defined complications of slow-flow, no-reflow and distal occlusion is illustrated as achievement of optimal myocardial blush grade and complete ST resolution (see text for definitions).

90%) and ST segment resolution 1 h after the procedure was not different between the two arms (15 vs. 17, p=0.59). The peak CK tended to be higher in patients undergoing TA (2601±276 vs. 1251±905, p=0.06). Acute stent thrombosis occurred in one patient assigned to the no TA group and in-hospital cardiac death in one patient in the TA group. At 6 month follow-up there was no significant differences in outcome between the groups.

3.2. Reproducibility of the residual in-stent atherothrombotic burden

Bland Altman plots for intra and interobserver variability are illustrated in Fig. 5. The variability and limits of agreement are good for this parameter as shown.

4. Discussion

The main findings of this study are that (1) OCT can be performed safely in patients presenting for primary PCI, (2) OCT allows detection of residual atherothrombotic material after stent implantation treated for STEMI even after use of thrombectomy devices. This is not appreciated by angiography. Moreover, OCT can quantify the amount of residual in-stent atherothrombotic material. (3) Patients with a high ATB as quantified by OCT are more likely to show angiographic complications of impaired flow including no reflow, slow flow, embolisation and distal occlusion than those with low atherothrombotic burden. Also these patients show reduced microvascular reperfusion as seen by a lower attainment of optimal myocardial blush grade and lower ST segment resolution.

From its conception to date, optical coherence tomography technology has undergone remarkable improvements that make its applicability to clinical practice a reality. Procedure safety is of particular importance in patients with unstable coronary artery disease especially patients with acute STEMI. OCT studies in this unstable patient population proved feasible with the first generation time domain imaging, though cumbersome. The development of Fourier domain second generation systems with short monorail OCT catheters that can be easily and quickly manoeuvred into the coronary artery, very fast pullbacks and the change from an occlusive technique to a flush technique that avoids induction of ischemia, has certainly improved the safety of this invasive imaging modality. Although embolisations of intraluminal atherothrombotic material may be perceived as a concern for applying this technique in patients, we did not observe any cases

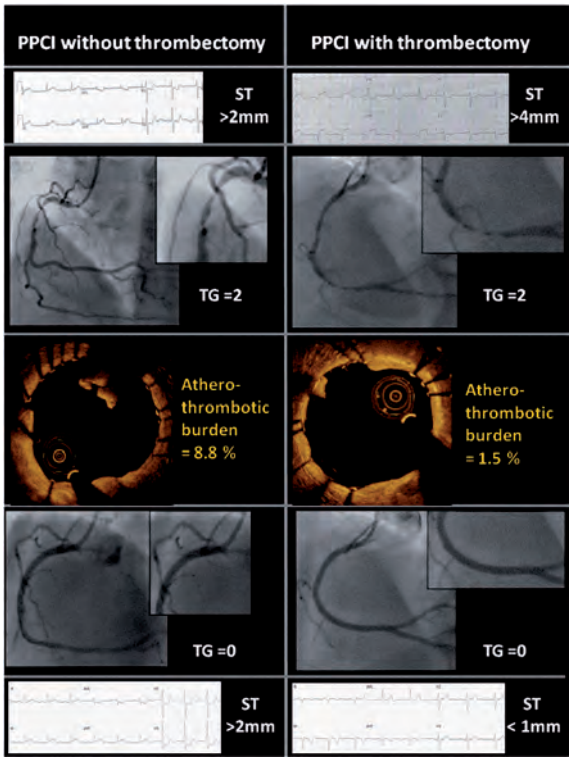


Fig. 3. OCT derived residual in-stent atherothrombotic burden and index of microvascular perfusion. Two patients presenting with an inferior myocardial infarction and enrolled in the study are shown here. The electrocardiograms (ECG) in the top panels show the degree of ST-segment elevation in the relevant leads. The patient on the left was randomised to treatment without thrombectomy while that on the right to treatment with thrombus aspiration. Angiographic thrombus grade after wiring was similar in both patients. Optical coherence tomography (OCT) after stenting showed a residual atherothrombotic burden of >4% in the patient without thrombectomy and a repeat ECG 1 h after the procedure showed failure of ST segment resolution (lower panel). The patient on the right had thrombus aspiration and OCT revealed a residual atherothrombotic burden of <4%. ECG at 1 h shows complete (>50%) ST segment resolution. Note that although both patients had no angiographically detected thrombus on the final angiogram (TG = 0), OCT in both patients detected residual atherothrombotic material.

that were clearly induced by the OCT catheter insertion or the contrast injection for blood clearance during pullback. Furthermore, high image quality can be reliably achieved and reproducibility of the measurements is very good as demonstrated in our study.

The sensitivity of thrombus detection by angiography is desirable as it may influence the need for adjunctive antithrombotic treatment. Higher thrombus load may require more aggressive or repeated use of thrombectomy, and antiplatelet or thrombolytic therapy. However thrombus load detection and quantification with the imaging modalities employed in daily practice for treatment of acute coronary syndromes have severe limitations [16]. Thrombus especially if mural is less likely to be detected by a luminogram and can be misinterpreted as stenotic plaque. This may lead to an underestimation of the thrombus load and perhaps also importantly overestimate the degree of coronary stenosis. The latter is important in intermediate or low grade stenosis in which stenting may not be necessary. In an earlier study, Kubo et al. have shown that in patients with acute myocardial infarction, intracoronary thrombus was observed in all cases by OCT and by coronary angioscopy, but it was identified in 33% by IVUS (vs. OCT, $p<0.001$) [14]. In their study, OCT was performed before stenting but after thrombectomy. This allowed assessment of the lesion and residual thrombus. Whether performing OCT at this stage prior to stenting poses a risk of embolisation of the residual atherothrombotic material is not yet known. Our positive safety results relate only to OCT pullbacks post-stenting and these results cannot be extrapolated to pre-stenting OCT procedures. From our experience, OCT performed prior to stent implantation in patients with either a high degree stenosis or a high thrombus load most often does not yield good quality images, mainly due to inadequate blood clearance. This would have resulted in exclusion of a significant number of patients, possibly limiting our analysis and conclusions. Also, since especially large thrombus in the lumen results in an optical shadow which restrains our ability to delineate the true endoluminal border behind it, this would compromise accurate and reproducible measurement of thrombus and of the other coronary structures. On the other hand with our methodology we used the ability of the stent to delineate the endoluminal border, leaving less room for

Table 2
Baseline clinical characteristics in patients with and without thrombus aspiration.

Characteristic	Thrombectomy n = 20	No thrombectomy n = 20	p value
Age (years)	61 ± 9	63 ± 12	0.84
Male	18 (90)	17 (85)	0.63
Diabetes			
Type 1	2 (10)	0 (0)	0.15
Type 2	2 (5)	1 (5)	0.55
Hypertension	7 (35)	7 (35)	1
Hypercholesterolaemia	10 (50)	5 (25)	0.10
Smoker			
Current	9 (45)	8 (40)	0.75
Ex	5 (25)	3 (15)	0.43
Family history of CAD	7 (35)	9 (45)	0.52
Previous MI	2 (10)	2 (10)	1
Previous PCI	1 (5)	0 (0)	0.31
Location of MI			
Anterior	10 (50)	5 (25)	0.10
Inferior	10 (50)	15 (75)	0.10
Ischaemic time, min	271 ± 247	326 ± 233	0.71
Pulse, bpm	72 ± 17	78 ± 21	0.48
Blood pressure, mmHg			
Systolic	126 ± 31	132 ± 29	0.54
Diastolic	76 ± 16	77 ± 15	0.96
Cardiogenic shock	1 (5)	0 (0)	0.31
Killip class 1	19 (95)	20 (100)	0.31

Categorical data are expressed as number (percentage) while continuous data are expressed as mean ± standard deviation. CAD = coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary intervention.

measurement variability. The correlation we found with residual in-stent atherothrombotic material and ST segment resolution supports the role thrombus and embolisation/microembolisation have in determining microvascular perfusion and infarct size. Both of the latter are important surrogate markers of mortality in patients treated for STEMI [6]. A reduction in residual atherothrombotic burden by mechanical or pharmacological means seems desirable and likely to improve myocardial perfusion. This novel index may therefore be used to assess the efficacy of future therapeutic options that target thrombus reduction in STEMI patients.

Table 3
Baseline angiographic characteristics in patients with and without thrombus aspiration.

Characteristics	Thrombectomy n = 20	No thrombectomy n = 20	p value
Infarct related artery			
LAD	10 (50)	6 (30)	0.20
LCx	2 (10)	3 (15)	0.63
RCA	8 (40)	11 (55)	0.34
TIMI flow presenting			
0	13 (65)	6 (30)	0.027
1	1 (5)	1 (5)	1
2	2 (10)	3 (15)	0.63
3	11 (55)	3 (15)	0.019
Thrombus grade after wiring			
1	1 (5)	5 (25)	0.08
2	7 (35)	7 (35)	1
3	9 (45)	7 (35)	0.52
4	2 (10)	1 (5)	0.55
5	1 (5)	0 (0)	0.31
Multivessel disease	11 (55)	12 (60)	0.75
MI SYNTAXscore	16 ± 8	11 ± 7	0.07
Lesion length, mm	19 ± 11	16 ± 11	0.23
Minimal luminal diameter, mm	1.11 ± 0.44	1.02 ± 0.47	0.81
Reference vessel diameter, mm	2.83 ± 0.47	2.75 ± 0.68	0.38
% diameter stenosis	60 ± 15	61 ± 15	0.86
cTFC after wiring	54 ± 32	45 ± 31	0.31

Data is expressed as mean ± standard deviation or number (percentage). LAD = left anterior descending coronary artery; LCx = left circumflex artery; RCA = right coronary artery. TIMI = thrombolysis in myocardial infarction flow grade; cTFC = corrected TIMI count. MI SYNTAXscore = myocardial infarction SYNTAXscore.

Table 4
Procedural characteristics in patients with or without thrombus aspiration.

Characteristic	Thrombectomy n = 20	No thrombectomy n = 20	p value
Aspiration runs	2 ± 1	0	<0.001
Macroscopic thrombus visible on sieve	5 (25)	–	0.57
Use of small balloon pre-stenting	3 (15)	5 (25)	0.43
Stent implanted			
EES	15 (75)	15 (75)	1
BMS	5 (25)	5 (25)	1
Number lesions with >1 stent	4 (20)	5 (25)	0.71
Total stent length, mm	31 ± 13	28 ± 17	0.14
Stent overlap	4 (20)	5 (25)	0.71
Postdilatation	11 (55)	8 (40)	0.34
GP IIb/IIIa inhibitors	12 (60)	9 (45)	0.34
Heparin units peri-procedural	5275 ± 1642	6000 ± 2051	0.23
Contrast used, mls	241 ± 69	207 ± 61	0.15
Procedure time, min	50 ± 15	39 ± 20	0.02

Data are expressed in mean ± standard deviation and number (percentage). EES = everolimus eluting stent; BMS = bare metal stent; GP = glycoprotein.

We found a non-significant trend toward a reduction in thrombus burden with thrombus aspiration. A reason for failure to reach statistical significance could be lack of power, that is low number in both groups. In order to detect a 30% (3.4–2.37) reduction in thrombus load by a thrombectomy device a sample size of at least 50 subjects is needed. Another reason could be the suboptimal use of the thrombectomy device or the actual suboptimal efficacy of the device. These reasons are plausible explanations of the lack of influence of TA in our study cohort on indices of myocardial perfusion.

The safety of drug eluting stent implantation in myocardial infarction has been questioned by some researchers and although this study was not designed to address this problem it offers some insights into this issue [17,18]. Previous observational studies have reported a higher incidence of malapposed stent struts at follow-up in patients with acute myocardial infarction when compared to patients with stable coronary artery disease [18]. Our study lends support to the hypothesis of the role of atherothrombotic burden. We observed a higher incidence of incomplete stent apposition in patients with a low TB. A large amount of thrombus can obscure our appreciation of whether stent struts are properly apposed to the true endolumen as opposed to apposition with mural thrombus. Resolution of mural thrombus may

Table 5
Optical coherence tomographic parameters in patients with and without thrombus aspiration.

OCT parameter	Thrombectomy n = 20	No thrombectomy n = 20	p value
Analysable pullbacks	20	20	1
ROI (stent length), mm	26 (20–32)	18 (15–25)	0.04
Mean lumen area, mm^2	9.29 ± 2.53	9.38 ± 2.78	0.87
Mean stent Area, mm^2	9.45 ± 2.73	9.64 ± 3.03	0.96
Minimal luminal area, mm^2	7.20 ± 2.46	7.47 ± 2.79	0.87
TROI, mm	20 (11–26)	12 (10–25)	0.21
Mean ATA, mm^2	0.24 (0.17–0.42)	0.36 (0.12–0.73)	0.46
Maximal ATA, mm^2	1.20 (0.92–1.91)	0.83 (0.53–2.05)	0.31
Free ATA, mm^2	0.00 (0.00–0.01)	0.00 (0.00–0.02)	0.67
Stent volume, mm^3	259 ± 137	210 ± 127	0.16
Atherothrombotic volume, mm^3	6.31 (3.20–1.57)	3.32 (2.04–15.0)	0.61
Atherothrombotic burden,%	2.37 (1.70–5.10)	3.40 (1.45–4.96)	0.67
ISA area, mm^3	0.046 (0.01–0.10)	0.049 (0.01–0.11)	0.88
ISA volume	1.31 (0.30–3.05)	0.92 (0.18–2.58)	0.72
% ISA	0.001	0.001	NS

Data is expressed in mean ± standard deviation and median (interquartile range). ROI = region of interest; TROI = atherothrombotic region of interest; ATA = atherothrombotic area; ISA = incomplete stent apposition.

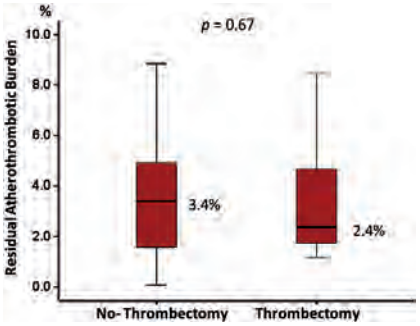


Fig. 4. In-stent atherothrombotic burden in patients treated with and without manual aspiration thrombectomy. Thrombus aspiration shows a trend toward a reduction in residual in-stent atherothrombotic burden which however did not reach statistical significance. Note that only 5 of the 20 patients in the thrombus aspiration arm had macroscopic thrombus retrieved on the sieve while none of the patients showed angiographic evidence of residual thrombus.

lead to ISA at follow-up. The relevance of this observation will need to be addressed in OCT studies with baseline and follow-up studies.

5. Limitations

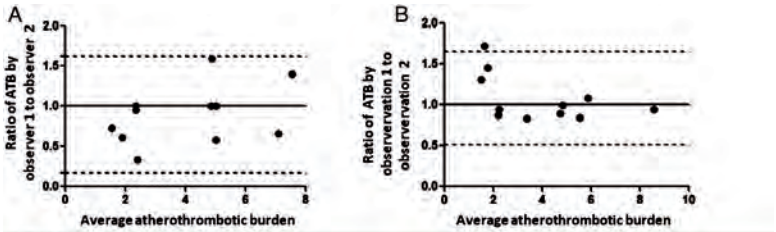
The study is an exploratory study and although we found a strong relation of residual in-stent atherothrombotic burden and indices of myocardial perfusion, the study was not sufficiently powered to assess its significance on hard clinical endpoints. The method we used to define atherothrombotic material has its limitations for a number of reasons. We use any intraluminal material within the TROI, limited within the stented segment to define atherothrombotic burden. This measure realistically includes both thrombus as well as atheromatous and plaque materials. However this is systematically and blindly done for all patients and should not affect the results or conclusions of our analysis. Measurement of thrombus before and after thrombectomy but before stenting by an imaging modality that does not interfere with the thrombus would be the best measure of the efficacy of thrombus aspiration. However in our study, OCT was performed after stenting and therefore the residual atherothrombotic burden may have been influenced by unaccounted interventions other than thrombus aspiration. This may have occurred despite our efforts in the study to minimise differences between the TA and non-TA groups except for thrombus aspiration. A randomised trial would be needed to confirm our findings. Analysis was done on an intention to treat basis which resulted in patients undergoing thrombectomy but without visible thrombus on the sieve. Although we did not do histopathological analysis of the aspirate, failure to retrieve macroscopic atherothrombotic material does not imply failure of thrombectomy and these patients may still have benefited from the adjunctive treatment [3].

6. Conclusions

OCT can detect and quantify residual atherothrombotic material after stent implantation in patients with acute STEMI. The residual in-stent atherothrombotic burden is associated with angiographic and ECG-derived markers of myocardial and microvascular perfusion. Incomplete stent apposition is less often detected in patients with high residual atherothrombotic material. These findings may be important surrogates of clinical outcome in patients treated with stent implantation for acute STEMI. Thrombus aspiration seems to lead to lower tissue protrusion in stent as quantified by OCT, possibly reflecting a reduction in the thrombus load. An adequately powered study is needed to confirm these findings.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [19].



Interobserver variability

	Observer 1	Observer 2	Absolute difference	Relative difference	Reproducibility	Limits of agreement Lower	Upper
ATB	4.30 ± 2.13	3.87 ± 2.43	0.43 ± 1.78	1.3	0.90	0.176	1.62

Intraobserver variability

	Observation 1	Observation 2					
ATB	3.80 ± 2.13	3.87 ± 2.43	-0.06 ± 0.58	1.1	1.1	0.51	1.62

Fig. 5. Reproducibility of in-stent atherothrombotic burden. Bland Altman plots and tables with limits of agreement for interobserver (A) and intraobserver (B) for measurement of residual in-stent atherothrombotic burden (ATB).

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Part VI

PERCUTANEOUS CORONARY INTERVENTIONS AND RISK STRATIFICATION IN PATIENTS WITH BYPASS GRAFTS

6.1

Long-term comparison of everolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for percutaneous coronary intervention of saphenous vein grafts.

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Long-term comparison of everolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for percutaneous coronary intervention of saphenous vein grafts

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KEYWORDS

- bypass graft
- drug-eluting stent
- paclitaxel-eluting stent
- sirolimus-eluting stent

Abstract

Aims: Newer-generation everolimus-eluting stents (EES) have been shown to improve clinical outcomes compared with early-generation sirolimus-eluting (SES) and paclitaxel-eluting stents (PES) in patients undergoing percutaneous coronary intervention (PCI). Whether this benefit is maintained among patients with saphenous vein graft (SVG) disease remains controversial.

Methods and results: We assessed cumulative incidence rates (CIR) per 100 patient years after inverse probability of treatment weighting to compare clinical outcomes. The pre-specified primary endpoint was the composite of cardiac death, myocardial infarction (MI), and target vessel revascularisation (TVR). Out of 12,339 consecutively treated patients, 288 patients (5.7%) underwent PCI of at least one SVG lesion with EES (n=127), SES (n=103) or PES (n=58). Up to four years, CIR of the primary endpoint were 58.7 for EES, 45.2 for SES and 45.6 for PES with similar adjusted risks between groups (EES vs. SES; HR 0.94, 95% CI: 0.55-1.60, EES vs. PES; HR 1.07, 95% CI: 0.60-1.91). Adjusted risks showed no significant differences between stent types for cardiac death, MI and TVR.

Conclusions: Among patients undergoing PCI for SVG lesions, newer-generation EES have similar safety and efficacy to early-generation SES and PES during long-term follow-up to four years.

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Abbreviations

ARC	Academic Research Consortium
BMS	bare metal stent(s)
CIR	cumulative incidence rates
DES	drug-eluting stent(s)
EES	everolimus-eluting stent(s)
HR	hazard ratio
IQR	interquartile range
MACE	major adverse cardiac events
MI	myocardial infarction
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PES	paclitaxel-eluting stent(s)
SD	standard deviation
SES	sirolimus-eluting stent(s)
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
SVG	saphenous vein graft
TVR	target vessel revascularisation
ULN	upper limit of normal

Introduction

Approximately 3-6% of percutaneous coronary interventions (PCI) are performed among patients with saphenous vein graft (SVG) disease[1], and this represents the most important revascularisation option for patients with graft failure. PCI of SVG lesions is characterised by high rates of restenosis and periprocedural myocardial infarction (MI) compared with revascularisation of native coronary arteries. Compared with bare metal stents (BMS), drug-eluting stents (DES) have been shown to reduce the risk of repeat revascularisation by 50%, related to a potent inhibition of neointimal tissue proliferation[2] without differences in terms of cardiac death or MI in the largest randomised trial performed to date[3,4]. However, early-generation DES releasing sirolimus (SES) or paclitaxel (PES) from durable polymers were used in two thirds of patients enrolled in this study[1], and little is known regarding the outcomes of newer-generation DES among patients with SVG disease. The newer-generation everolimus-eluting stent (EES) is a thin-strut, cobalt-chromium alloy stent, which is coated with a durable, fluorinated co-polymer releasing a reduced dose of everolimus compared to the dose used with SES[5]. EES have been shown to improve efficacy and safety compared with early-generation PES[6-8] through two years and to provide similar efficacy but improved safety compared with early-generation SES[9,10] in a wide range of patients and lesions. However, it is unknown whether the favourable results with the use of newer-generation EES remain sustained among patients undergoing PCI for SVG disease. We therefore investigated the long-term clinical outcomes of patients undergoing PCI of SVG lesions with the use of EES compared with SES and PES in a large-scale registry.

Methods

PATIENT POPULATION

The Bern-Rotterdam registry evaluates clinical outcomes of patients treated with the unrestricted use of DES enrolled at Bern University Hospital, Bern, Switzerland, and the Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands.

Primary results with focus on stent thrombosis have been reported previously[6,7,11]. In the Dutch institution, SES had been used as a default strategy for PCI as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, PES became commercially available and replaced SES as default device and became part of the TAXUS Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. EES (XIENCE V®; Abbott Vascular, Santa Clara, CA, USA, or PROMUS®; Boston Scientific, Natick, MA, USA) had been used as a default strategy for PCI as part of the XIENCE Stent Evaluated At Rotterdam Cardiology Hospital (X-SEARCH) registry since March 1, 2007, until the end of this study period. In the Swiss institution, EES had been used since November 1, 2006, and were implanted on a daily basis alternating with biolimus-eluting stents and zotarolimus-eluting stents. SES had been used since April, 2002, and PES since March, 2003. Individual patients who had been treated with more than one type of DES were excluded from the current registry. The study was approved by the local ethics committee at both institutions and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

DATA COLLECTION

All patients were actively followed for major adverse cardiac events using patient administered postal questionnaires including questions on rehospitalisation and major adverse cardiac events. This was complemented by a search of hospital databases at the two institutions. In Bern, the last follow-up took place from February 1, 2007, onwards for patients who had undergone implantation of SES or PES and from February 1, 2010, onwards for patients with EES. In Rotterdam, the last follow-up took place from July 1, 2005, onwards for patients with PES, July 1, 2006, for patients with SES, and April 1, 2010, onwards for patients with EES, respectively. For patients with a suspected event, relevant medical records, discharge letters, and coronary angiography documentation were systematically collected. All suspected clinical events were adjudicated by local cardiologists affiliated with the two institutions, whereas all ST events were adjudicated by an independent clinical events committee whose members were unaware of the type of stent implanted. Baseline clinical and procedural characteristics and all follow-up data were entered into a dedicated database, held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Bern, Switzerland) responsible for central data audits and maintenance of the database.

PROCEDURES

EES were available in diameters from 2.25 to 4.0 mm and in lengths from 8 to 28 mm; SES were available in diameters from 2.25 to 3.5 mm and in lengths from 8 to 33 mm, and PES were available in diameters from 2.25 to 4.0 mm and in lengths from 8 to 32 mm. The procedure and treatment including peri- and post-procedural

medication regimen were performed according to current practice guidelines. All patients irrespective of stent type received a loading dose of clopidogrel 300 mg to 600 mg during or immediately after the procedure and were prescribed aspirin once daily lifelong. In the Dutch institution, clopidogrel was administered to patients with SES for at least three months, and for at least six months if patients had received three or more stents, the total stent length was >36 mm, or a chronic total occlusion or bifurcation was treated. Dutch patients treated with EES were prescribed clopidogrel for 12 months. In the Swiss institution, all patients were prescribed clopidogrel for a duration of at least 12 months irrespective of stent type. The use of glycoprotein IIb/IIIa antagonists and distal protection devices was left at the discretion of the operator.

DEFINITIONS

The primary endpoint of this study was major adverse cardiac events (MACE) defined as the composite of cardiac death, MI, and target vessel revascularisation up to four years. The definition of cardiac death included any death due to immediate cardiac cause, procedure-related deaths, unwitnessed death and death of unknown cause. The diagnosis of MI was based on an elevation in CK to more than twice the upper limit of normal (ULN) and an elevation of CK-MB to more than three times ULN in the presence of ischaemic symptoms or ischaemic ECG changes. Target vessel revascularisation (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment within the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself. Target lesion revascularisation (TLR) was defined as a repeated revascularisation due to a stenosis within the stent or within the 5 mm borders proximal or distal to the stent. A 12-lead electrocardiogram was obtained prior to the procedure and within 24 hours after PCI. Additional ECGs were obtained in case of recurrent signs or symptoms of ischaemia. Acute coronary syndrome was defined as acute myocardial ischaemia based on clinical symptoms, electrocardiographic changes, and elevation of cardiac biomarkers, and encompassed an acute ST-segment (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina. Definitions of hypertension, hyperlipidaemia and renal dysfunction were reported previously[7,11]. Stent thrombosis was defined according to the Academic Research Consortium (ARC)[8,9].

STATISTICAL ANALYSIS

Baseline clinical and procedural characteristics of the three stent types are presented as counts and percentages for dichotomous variables and as mean and standard deviation (SD) for continuous variables. Pearson's chi-square test and Student's t-test were used for comparing dichotomous and continuous variables, respectively. Cumulative incidence rates (CIR) per 100 patient years were calculated for each endpoint, defined as the number of new events occurring during a specific time period divided by the total number of patient years observed. In contrast to crude percentages, CIR take into account differences in follow-up duration between different stent types. Propensity scores for receiving EES were estimated for each centre by the use of a logit model including age, gender and pre-treatment variables associated with stent selection at $p<0.10$ (i.e., family history of coronary artery disease, acute coronary syndrome and cardiogenic shock for both centres; body mass index and left ventricular ejection fraction as additional variables for Bern; arterial hypertension, smoking, diabetes and hyperlipidaemia as additional variables for Rotterdam). Propensity scores were used to derive inverse probability of treatment weights, with the inverse of propensity score as analytical weights in EES-treated patients and the inverse of 1 minus the propensity score among early-generation DES-treated patients. Comparisons between stent types were performed with a Cox proportional hazards model, crude and adjusted using inverse probability of treatment weighting. All statistical analyses were performed using STATA release 11.1 (Stata Corp., College Station, TX, USA). All p-values are two-sided.

Results

Between April 16, 2002, and March 31, 2009, 12,339 consecutive patients underwent treatment with the unrestricted use of EES (n=4,212), SES (n=3,819) and PES (n=4,308). Out of this cohort, 288 patients (5.7%) (177 [61.5%] enrolled at Bern University Hospital, and 111 [38.5%] included at Thoraxcenter, Rotterdam) underwent PCI of at least one SVG lesion with the use of EES among 127 patients, SES among 103 patients, and PES among 58 patients. Baseline clinical characteristics for all three stent types are summarised in **Table 1**. Patients treated with EES compared with those treated with either SES or PES more frequently had diabetes. Patients treated with EES were more frequently hypertensive compared to those treated with PES, and more frequently had dyslipidaemia, renal failure and presented with an acute coronary syndrome than SES-treated patients. **Table 2** shows procedural characteristics, which were balanced among the three treatment groups with the exception of a larger stent diameter in lesions treated with EES compared with those treated with SES. The use of glycoprotein IIb/IIIa antagonists, aspirin, and proton pump inhibitors was more frequent among EES compared with PES-treated patients.

Clinical outcome

The median follow-up duration among surviving patients completing the last follow-up was 2.5 years in patients treated with EES (interquartile range: IQR 1.9 to 3.2 years), four years in patients treated with SES (IQR 3.0 to 4.0 years), and 3.5 years in patients treated with PES (IQR 2.3 to 4.0 years) with an accumulated 144, 266, and 302 patient years, respectively.

Clinical outcomes up to four years are summarised in **Table 3** and **Table 4**.

Up to four years, incidence rates per 100 patient years for the primary endpoint MACE were similar among patients treated with EES (58.7%), SES (45.2%, adjusted HR 0.94, 95% CI: 0.55-1.60) and PES (45.6%, adjusted HR 1.07, 95% CI: 0.60.-1.91) in adjusted analyses (**Table 3** and **Table 4**, **Figure 1**). Similarly, there was no difference in the risk of cardiac death (EES vs. SES adjusted HR 1.18, 95% CI: 0.49-2.84, EES vs. PES adjusted HR 0.81, 95% CI: 0.30-2.17),

Table 1. Baseline clinical characteristics.

	Stent type			*p*-value	
	EES (A)	SES (B)	PES (C)	A vs. B	A vs. C
Number of patients	127	103	58		
Age (yr)	69.2 (9.6)	67.5 (10.5)	68.3 (8.8)	0.19	0.54
Male gender	104 (81.9)	86 (83.5)	53 (91.4)	0.75	0.09
Body mass index (kg/m^2)	27.7 (3.6)	27.2 (3.7)	27.4 (3.8)	0.27	0.64
Hypertension	89 (70.1)	67 (65.0)	28 (48.3)	0.42	0.004
Family history of CAD	44 (34.6)	33 (32.0)	18 (31)	0.68	0.63
Smoking at baseline	43 (33.9)	47 (45.6)	24 (41.4)	0.07	0.32
Dyslipidaemia	101 (79.5)	69 (67.0)	39 (67.2)	0.031	0.07
Diabetes mellitus	46 (36.2)	18 (17.5)	11 (19)	0.002	0.018
Renal failure (GFR <60 ml/min)*	12 (21.4)	11 (13.4)	8 (20.5)	0.21	0.91
Renal failure (creatinine >150 µmol/l)*	4 (7.1)	0 (0)	2 (5.1)	0.014	0.69
Left ventricular ejection fraction, <30%	3 (6.3)	6 (7.8)	3 (8.8)	0.75	0.66
Acute coronary syndrome	74 (58.3)	39 (37.9)	26 (44.8)	0.002	0.09
Unstable angina/non-ST-elevation MI	57 (77.0)	34 (87.2)	23 (88.5)	0.20	0.21
ST-elevation MI	17 (23.0)	5 (12.8)	3 (11.5)	–	–
Cardiogenic shock	1 (0.8)	0 (0)	0 (0)	0.37	0.50

Values are n (%) or mean±SD. *data only available in Bern patients. Comparisons between groups among dichotomous variables were performed using Pearson's chi-square test and Student's t-test for continuous variables. CAD: coronary artery disease; EES: everolimus-eluting stent; GFR: glomerular filtration rate; MI: myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

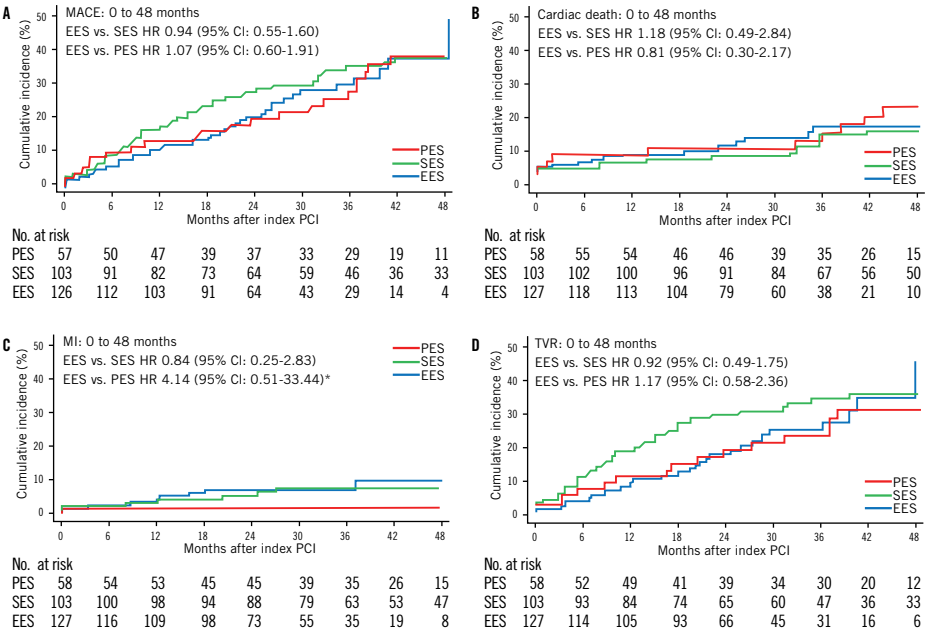

Figure 1. *Cumulative event curves for the primary endpoint of major adverse cardiac events (MACE) (A), cardiac death (B), myocardial infarction (MI) (C), and target vessel revascularisation (TVR) (D) up to 48 months. EES: everolimus-eluting stents; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents *Crude hazard ratio is shown, as adjusted model did not converge.*

Table 2. Baseline procedural characteristics.

	Stent type			*p*-value	
	EES (A)	SES (B)	PES (C)	A vs. B	A vs. C
Total (n)	127	103	58		
Multivessel treatment	20 (15.7)	22 (21.4)	11 (19.0)	0.27	0.59
Number of vessels treated per patient	1.2 (0.4)	1.2 (0.6)	1.2 (0.4)	0.29	0.80
Number of lesions treated per patient	1.4 (0.6)	1.4 (0.8)	1.3 (0.5)	0.68	0.34
1 lesion	40 (71.4)	55 (67.1)	30 (76.9)	–	–
2 lesions	11 (19.6)	19 (23.2)	8 (20.5)	–	–
3 lesions	5 (8.9)	4 (4.9)	1 (2.6)	–	–
Number of stents per patient	1.9 (1.1)	2.1 (1.2)	1.8 (1.0)	0.33	0.41
Average stent diameter	3.2 (0.5)	3 (0.3)	3.2 (0.5)	0.0002	0.35
Total stent length per patient	32.4 (23.0)	37.6 (24.4)	33.1 (26.5)	0.10	0.86
Glycoprotein IIb/IIIa antagonist	26 (20.5)	14 (13.6)	2 (3.4)	0.17	0.003
Medication at discharge					
Aspirin	123 (100)	99 (98.0)	56 (96.6)	0.12	0.038
Clopidogrel	123 (100)	99 (99.0)	57 (98.3)	0.27	0.14
Oral anticoagulation	7 (5.7)	6 (5.9)	7 (12.1)	0.94	0.13
Beta-blocker	37 (66.1)	54 (67.5)	25 (64.1)	0.86	0.84
ACE inhibitor	23 (41.1)	39 (48.8)	18 (46.2)	0.38	0.62
AT II inhibitor	10 (17.9)	17 (21.3)	4 (10.3)	0.63	0.30
Calcium antagonist	12 (21.4)	18 (22.5)	11 (28.2)	0.88	0.45
Statin	52 (92.9)	69 (86.3)	33 (84.6)	0.23	0.20
Oral antidiabetic	8 (14.3)	12 (15.0)	2 (5.1)	0.91	0.15
Insulin	5 (8.9)	3 (3.8)	5 (12.8)	0.21	0.54
Diuretics	18 (32.1)	20 (25.0)	13 (33.3)	0.36	0.90
Proton pump inhibitor	21 (37.5)	20 (25.0)	6 (15.4)	0.12	0.019

Values are n (%) or mean±SD. Comparisons between groups among dichotomous variables were performed using Pearson's chi-square test and Student's t-test for continuous variables. Number of patients on discharge medication is based on the number of patients alive at discharge. EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

MI (EES vs. SES adjusted HR 0.84, 95% CI: 0.25-2.83, EES vs. PES crude HR 4.14, 95% CI: 0.51-33.44), and TVR (EES vs. SES adjusted HR 0.92, 95% CI: 0.49-1.75, EES vs. PES adjusted HR 1.17, 95% CI: 0.58-2.36) in adjusted analyses. The incidence rates per 100 patient years for definite ST and definite or probable ST showed no differences among stent types at any time point **(Table 5)**.

Table 3. Clinical outcome at 1 year.

	Stent type			Adjusted analysis			
				A vs. B		A vs. C	
	EES (A)	SES (B)	PES (C)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Number of patients	127	103	58				
All-cause death	13 (10.4)	3 (2.9)	4 (7.0)	3.71 (1.06-13.03)*	0.04*	1.50 (0.49-4.60)*	0.48*
Cardiac death	7 (5.8)	3 (2.9)	3 (5.3)	1.18 (0.20-7.05)	0.85	0.89 (0.21-3.81)	0.87
MI	4 (3.4)	3 (2.9)	1 (1.8)	0.70 (0.13-3.73)	0.68	0.47 (0.03-7.40)	0.59
TLR	7 (6.1)	11 (10.8)	3 (5.6)	0.43 (0.12-1.50)	0.18	0.73 (0.17-3.16)	0.68
TVR	10 (8.6)	17 (16.7)	5 (9.3)	0.34 (0.10-1.13)	0.08	0.55 (0.17-1.80)	0.32
Cardiac death/MI	11 (9.0)	5 (4.9)	4 (7.0)	1.46 (0.43-5.01)	0.55	0.93 (0.26-3.33)	0.91
Cardiac death/MI/TLR	15 (12.3)	15 (14.6)	7 (12.3)	0.71 (0.30-1.70)	0.45	0.75 (0.28-1.99)	0.56
Cardiac death/MI/TVR	17 (13.9)	21 (20.4)	9 (15.8)	0.53 (0.23-1.23)	0.14	0.63 (0.26-1.50)	0.29

Clinical outcome numbers are expressed as counts and incidence rates per 100 patient years. Adjusted risk ratios were calculated using inverse probability of treatment weights as analytical weighting in Cox proportional hazard models. *Crude rates are shown, as adjusted model did not converge. CI: confidence interval; EES: everolimus-eluting stent; HR: hazard ratio; MI: myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target lesion revascularisation; TVR: target vessel revascularisation

Table 4. Clinical outcome up to 4 years.

	Stent type			Adjusted analysis			
				A vs. B		A vs. C	
	EES (A)	SES (B)	PES (C)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Number of patients	127	103	58				
All-cause death	22 (21.5)	19 (19.5)	11 (24.8)	1.01 (0.52-1.97)	0.98	0.94 (0.41-2.14)	0.88
Cardiac death	14 (15.3)	12 (13.2)	9 (21.8)	1.18 (0.49-2.84)	0.71	0.81 (0.30-2.17)	0.67
MI	8 (9.1)	8 (8.5)	1 (1.8)	0.84 (0.25-2.83)	0.77	4.14 (0.51-33.44)*	0.18*
TLR	19 (25.8)	26 (27.6)	6 (12.6)	0.73 (0.35-1.53)	0.40	1.58 (0.57-4.35)	0.38
TVR	28 (52.0)	34 (35.5)	14 (31.0)	0.92 (0.49-1.75)	0.81	1.17 (0.58-2.36)	0.67
Cardiac death/MI	21 (21.8)	19 (20.3)	10 (23.2)	1.01 (0.48-2.10)	0.99	0.95 (0.38-2.41)	0.92
Cardiac death/MI/TLR	34 (37.9)	36 (37.6)	15 (32.0)	0.87 (0.49-1.56)	0.65	1.16 (0.59-2.31)	0.66
Cardiac death/MI/TVR¶	40 (58.7)	44 (45.2)	22 (45.6)	0.94 (0.55-1.60)	0.82	1.07 (0.60-1.91)	0.81

¶Composite primary endpoint. Clinical outcome numbers are expressed as counts and incidence rates per 100 patient years. Adjusted risk ratios were calculated using inverse probability of treatment weights as analytical weighting in Cox proportional hazard models. *Crude rates are shown, as adjusted model did not converge. CI: confidence interval; EES: everolimus-eluting stent; HR: hazard ratio; MI: myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target lesion revascularisation; TVR: target vessel revascularisation

The duration of dual antiplatelet therapy differed between the two institutions. In order to analyse potential site-specific differences in outcomes comparing EES with early-generation DES, we performed a sensitivity analysis for the primary outcome and found hazards to be similar for both institutions regarding the primary endpoint (Bern EES vs. early-generation DES: HR 0.94, 95% CI: 0.55-1.60, p=0.82; Rotterdam EES vs. early-generation DES: HR 1.07, 95% CI: 0.60-1.01, p=0.82).

Discussion

This is the first report comparing newer-generation EES with early-generation SES and PES during long-term follow-up among patients undergoing PCI for SVG disease. The main findings of our study are: 1) the use of EES resulted in similar safety and efficacy compared to the use of early-generation SES and PES among patients with SVG lesions; 2) event rates for restenosis and recurrent ischaemia were exceedingly high during follow-up through four years regardless of the type of DES implanted.

Limited data are available on the treatment of SVG lesions with coronary artery stents.

A comparison of DES with BMS in SVG lesions in a total of 5,543 patients followed for at least one year yielded similar results to those observed in other patient populations, namely a substantial improvement in the need for repeat revascularisation of the target vessel without differences in terms of MI or stent thrombosis. Differences in cardiac death were not recorded when taking into account only randomised trials[12]. However, conflicting results were observed among the few studies investigating outcomes beyond one year. The randomised Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent (DELAYED RRICS) study suggested an increased risk of cardiac death and numerically lower rates of MI with SES compared with BMS as well as a loss of the initially observed lower risk of TVR during long-term follow-up. Conversely, the long-term results of the Stenting of Saphenous Vein Grafts (SOS) trial suggested a similar risk of cardiac death but a lower risk of MI as well as sustained efficacy in terms of repeat revascularisation among PES compared with BMS-treated patients with SVG disease during long-term follow-up.

Newer-generation DES have been designed to improve upon the limitations of early-generation DES by reducing stent strut thickness, increasing the biocompatibility of polymers and modifying drug content. Several randomised clinical trials as well as large-scale registries confirmed improved safety and efficacy of

Table 5. Definite or definite/probable stent thrombosis up to 4 years.

	Stent type			Adjusted analysis			
				A vs. B		A vs. C	
	EES (A)	SES (B)	PES (C)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Number of patients	127	103	58				
Definite stent thrombosis	4 (4.0)	3 (3.1)	1 (2.2)	1.28 (0.29-5.74)*	0.74*	0.88 (0.10-8.03)	0.91
Definite or probable stent thrombosis	9 (10.1)	9 (9.5)	3 (5.7)	0.79 (0.24-2.61)	0.69	0.90 (0.22-3.64)	0.89

Clinical outcome numbers are expressed as counts and incidence rates per 100 patient years. Adjusted risk ratios were calculated using inverse probability of treatment weights as analytical weighting in Cox proportional hazard models stratified by centre. *Crude rates are shown, as adjusted model did not converge. CI: confidence interval; HR: hazard ratio; EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

newer-generation EES compared with PES and SES in a wide range of patient and lesion subsets. To date, only one study has compared early-generation DES with a newer-generation stent releasing sirolimus from a biodegradable polymer among patients undergoing treatment of SVG lesions and observed no difference in terms of the primary endpoint including cardiac death, MI, and repeat revascularisation[13]. As it relates to long-term results, no data are available at this point in time.

Our study is the first to compare newer-generation EES with early-generation SES and PES among patients undergoing PCI of SVG lesions during long-term follow-up through four years, and is of particular interest due to the unselected, consecutive patient population undergoing PCI with the unrestricted use of DES. Similar to outcomes in ISAR-CABG, outcomes for the primary endpoint and its individual components were similar for newer-generation DES compared with early-generation SES and PES. Even when considering device-specific endpoints such as cardiac death, MI and TLR as well as stent thrombosis, no differences were noted among these devices throughout the entire follow-up period.

Irrespective of stent type, adverse events were much more frequent among patients undergoing PCI of SVG lesions compared to those undergoing PCI of native coronary arteries. Specifically, rates of MACE at four years in the present study (46%) were similar to those reported among PES-treated patients in the randomised Stenting of Saphenous Vein Grafts (SOS) trial at 35 months of follow-up (54%)[14]. Similarly, in the Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent (DELAYED RRICS) study[15], rates of MACE amounted to 58% among SES-treated patients at a median follow-up of 32 months. These figures contrast with rates of MACE in the range of 20% among unselected patients enrolled in all-comers studies with the predominant treatment of native coronary artery lesions[16-18]. Of note, clinical outcomes were driven by high rates of death, restenosis of the target lesion as well as disease progression within the target vessel, reflecting the advanced stage of coronary artery disease in this patient population.

Potential explanations for the lack of benefit with newer-generation EES compared with early-generation DES in the specific subset of SVG lesions may have been the small patient population. However, considering the high event rates and the long-term follow-up, hazards would be expected to favour EES, assuming similar benefits in terms of relative risk reduction observed in pivotal trials and all-comer patient populations. Differences between SVG lesions and native coronary arteries in terms of periprocedural treatment characteristics, atherosclerotic disease burden as well as the interaction with revascularisation by means of drug-eluting stents may be of relevance. Brilakis and colleagues reported an increased risk for in-hospital mortality among patients undergoing PCI for treatment of SVG compared to native coronary artery lesions (HR 1.22, 95% CI: 1.12-1.32, p<0.001). This was related to differences in patient and lesion risk profile and a higher incidence of acute complications such as no reflow[19]. SVG failure remote from the stented lesion (TVR without TLR) occurs in 30-50% of all repeat revascularisation procedures. This proportion is certainly higher compared with lesions involving native coronary arteries[20,21], suggesting that non-stented disease progression remains an important adverse event among patients with SVG disease. Although rates of target lesion revascularisation during the first year in the present study were very much comparable to those observed following treatment of native coronary artery lesions, recurrent ischaemia related to the stented segment became increasingly apparent at a later time, suggesting a considerable lack of long-term efficacy. Specifically, annual rates of TLR between the first and fourth year of follow-up were 50 to 70% higher compared with annual rates previously reported in the context of native coronary artery disease[16]. Therefore, SVG lesions continue to represent an important lesion subset with inadequate efficacy following the use of newer-generation DES.

Pathological analyses and experimental animal models have contributed to our understanding of accelerated atherosclerosis in SVG lesions[22]. Mechanical stress induced by a substantial change in haemodynamics from a venous to an arterial circulation has been identified as an important source of saphenous vein graft wall thickening, largely related to gene expression of adhesion molecules, which evoke inflammatory processes and signal pathways resulting in proliferative cell growth. Neointimal formation is followed by macrophage infiltration and eventually necrotic core formation, resulting in vulnerable plaque formation. Stent implantation of SVG lesions more often lead to strut penetration into the necrotic core, which may delay healing and perpetuate inflammation, compared with stents implanted into native coronary artery lesions resulting in an increased risk for thrombotic occlusions[23]. In addition, neoatherosclerotic changes have been observed as early as one year after stent implantation in SVG lesions, which is more premature than observed in native coronary artery lesions. Although the prevalence of neoatherosclerosis within DES-treated SVG lesions has not been assessed to date, pathology studies suggest that neoatherosclerosis is an important mechanism contributing to restenosis during long-term follow-up, providing a potential explanation for the high TLR rates observed in this study beyond one year.

Very late stent thrombosis is one of the major concerns with the use of early-generation DES; however, the use of EES was associated with a substantial reduction in an all-comers patient population[9,10]. In the present study, there were no differences among the three stent platforms. However, event rates and patient population were small, precluding further exploration of differences among devices.

Limitations

The present study has to be interpreted in view of the following limitations. First, this study was not specially designed to compare the safety and efficacy of newer-generation EES with early-generation DES in SVG lesions. The data are derived from a non-randomised, observational cohort. Second, we lack information regarding the diameter of SVG lesions, the use of distal protection devices, and the age of SVGs at the time point of the intervention. Third, patients were enrolled during different time periods and advances in interventional

techniques (e.g., more frequent post-dilatation) may have impacted on results. In addition, the follow-up period differed among the three treatment groups. However, we employed statistical methodologies to present adjusted analyses by employing inverse probability of treatment weights and the reporting of cumulative incidence rates. Finally, the sample size of this study is small; larger patient populations are needed to address more definitively the value of newer-generation DES in SVG lesions.

Conclusions

Among patients undergoing PCI for SVG lesions, newer-generation EES provide similar safety and efficacy compared to early-generation SES and PES during long-term follow-up. The high rates of adverse events among patients with SVG disease are related to disease progression of treated and untreated SVG segments.

Guest Editor

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Conflict of interest statement

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6.2

Seven-year safety and efficacy of the unrestricted use of drug-eluting stents in saphenous vein bypass grafts.

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Seven-Year Safety and Efficacy of the Unrestricted Use of Drug-Eluting Stents in Saphenous Vein Bypass Grafts

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Objectives: The aim was to investigate the 7-year clinical outcomes of patients treated with either drug-eluting stents (DES) or bare-metal stents (BMS) for saphenous vein graft disease (SVG). Background: Atherosclerotic disease in SVG has several peculiarities which make it difficult to extrapolate outcomes of the use of DES as compared to BMS, from outcomes observed in native coronary arteries. To date no long-term safety and efficacy results for DES in SVG have been published. Methods: Between January, 2000 and December, 2005 a total of 250 consecutive patients with saphenous vein graft disease were sequentially treated with DES (either sirolimus- or paclitaxel-eluting stents) or with BMS. Yearly follow-up was performed. Results: At 87 months (7.25 years), a total of 101 patients died (58 [46%] in the BMS group and 43 [42%] in the DES group, *P*-value= 0.4). There was no significant difference in the combined endpoint mortality or myocardial infarction. Cumulative target vessel revascularisation (TVR) was higher in the BMS group compared to the DES group (41% vs. 29%, respectively; adjusted hazard ratio [HR] 0.63, 95% confidence interval [CI]: 0.39–1.0). The cumulative incidence of major adverse cardiac events was 73% vs. 68% in the BMS and DES groups, respectively (adjusted HR 0.93, 95% CI: 0.67–1.3). Conclusions: In the present study, the unrestricted use of DES for SVG lesions appeared safe and effective up to 7.25 years- and the use of DES resulted in a clinically relevant lower rate of TVR.

Key words: coronary artery bypass; survivors; cardiology

INTRODUCTION

Coronary artery bypass graft surgery (CABG) often involves saphenous vein graft (SVG) conduits [1]. However, the lifespan of SVG has proven to be limited—at 10 years, 50% of such grafts contain at least one significant stenosis [2]. Significant atherosclerotic disease of SVG, despite optimal medical therapy, may result in the recurrence of symptoms and a higher risk of major adverse cardiac events necessitating re-intervention [1].

Given the high risk of redo-surgery, [3] and the availability of new technologies including embolic protection devices and dedicated catheters, PCI with bare-metal stents (BMS) has surpassed CABG as the treatment of first choice for treating saphenous vein graft disease [4,5]. Still, the cumulative event rate after stent implantation remains high because of atherosclerotic disease progression and in-stent restenosis [6,7]. Earlier the RRISC trial showed a catch-up in the repeat revascularization rates in patients treated with sirolimus-eluting stents (SES). Moreover, the authors reported significant increase in late mortality in patients treated with SES as compared to those treated with BMS [8].

Atherosclerotic disease in SVG has several peculiarities—including the plaque composition and restenotic process [9–12]—that differ from native coronary arteries. Therefore, it is uncertain whether the

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beneficial effects of drug-eluting stents (DES) compared to BMS in native coronary arteries could be extrapolated to SVGs. The safety and efficacy for DES in SVG has been proven for clinical outcomes up to 3 years in multiple meta-analyses [13–21]. However, no study reports the long-term outcomes after DES in SVG.

We therefore set out to investigate the long-term safety and efficacy outcomes (up to 7 years) of a consecutive series of patients treated with BMS or DES for lesions in saphenous vein grafts.

METHODS

Patient Selection

Between January 1, 2000 and December 31, 2005 a total of 250 percutaneous coronary interventions were performed in our institution using BMS ($n = 128$), SES ($n = 21$), or paclitaxel-eluting stent (PES; $n = 101$) in saphenous vein graft lesions. Patients who received previous brachy therapy ($n = 27$) and patients who received no stent ($n = 35$) or a Symbiot^{TM} Covered Stent ($n = 2$) are not included in this number.

All patients remained in their first original enrolled cohort during the follow-up period. The BMS subgroup contained all consecutive patients before April 16, 2002. On 16th of April our institution commenced the unrestricted use of drug-eluting stents as default strategy. Until January 2003 SES (Cypher^{R}, Cordis Corp., Johnson & Johnson, Warren, NJ) were used exclusively, whereas from February 2003 PES (TAXUS^{TM}, Express2^{TM} or Liberté^{TM}, Boston Scientific, Natick, MA) replaced the SES as the device of choice for every percutaneous coronary intervention—including vein graft interventions. This study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki.

All procedures were performed according to standard procedural guidelines and their details have been reported previously [22]. Every patient was pre-treated with aspirin and $\geq$300 mg clopidogrel. Angiographic success was defined as residual stenosis $\leq$30% by online quantitative coronary angiography in the presence of Thrombolysis In Myocardial Infarction flow grade 3. All patients were advised to maintain aspirin lifelong and clopidogrel for at least 1 month if BMS were used, for $\geq$3 months for patients with SES, and $\geq$6 months for patients with PES. Distal embolization protection devices and peri-procedural glycoprotein IIb/IIIa inhibitors were used according to the operator's discretion.

Definitions and Clinical Endpoints

Definitions of baseline characteristics are according to the RESEARCH and T-SEARCH registry definitions, and have previously been described [22,23].

Safety end-points included all-cause mortality, the composite of all cause mortality/myocardial infarction (MI) and stent thrombosis, whereas the efficacy end point consisted of target vessel revascularization (TVR). The combined endpoint major adverse cardiac event (MACE) was defined as a composite of all-cause mortality, any MI related or unrelated to TVR stenting and TVR.

MI was diagnosed by recurrent symptoms and/or new electrocardiographic changes in association with a concomitant rise and fall in creatinin kinase-MB mass or troponin-T/ troponin-I to $\geq$3 times the upper limit of normal. A TVR was defined as a percutaneous or surgical re-intervention driven by any lesion ($\geq$50% of the luminal diameter) located in the index graft, in the presence of ischemic symptoms, or a positive functional ischemia study. Stent thrombosis was defined as angiographically defined thrombosis with Thrombolysis In Myocardial Infarction flow grade 0 or 1 or the presence of a flow limiting thrombus, accompanied by acute onset of ischemic symptoms at rest, similar to the ARC definite criteria [22,24].

Survival status was assessed through municipal civil registries. A prospectively developed questionnaire inquiring about patients' current health status, clinical events, and medication use was sent to all living patients on a yearly basis. In case of an event, medical records, discharge summaries and, when necessary, angiographic films, were systematically reviewed. Cause of death was acquired via the Central Bureau of Statistics, The Hague, The Netherlands or by directly contacting the patients' General Physician [22].

Statistical Analysis

Continuous variables are presented as mean and standard deviation or as median and boundary of interquartile range, categorical variables as absolute numbers and percentage. Normality assumption was evaluated by the Kolmogorov-Smirnov test. Continuous variables were compared using Student's unpaired *t* test or Mann-Whitney non-parametric test. Categorical variables were compared using chi-square statistics or Fischer's exact test, as appropriate.

The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method, and curves were compared using log-rank test. Observed unadjusted and adjusted measures of association were obtained by Cox regression models and presented as hazard ratios. Because of the total number of events

TABLE I. Baseline and Procedural Characteristics Stratified According to Stent Type

	BMS ($n = 128$)	DES ($n = 122$)	P-value
Male, n (%)	102 (80%)	103 (84%)	0.33
Age, mean ± SD	69 ± 9.6	68 ± 8.7	0.31
Cardiac history			
Previous MI	59 (46%)	61 (50%)	0.23
Previous PCI	34 (27%)	36 (30%)	0.77
Risk factors			
Diabetes mellitus	27 (21%)	38 (31%)	0.07
Hyperlipidaemia	57 (45%)	81 (66%)	0.001
Hypertension	55 (43%)	60 (49%)	0.33
Family history of CAD	22 (17%)	34 (28%)	0.043
Current smoker	21 (16%)	10 (8%)	0.049
Renal impairment	2 (2%)	6 (5%)	0.13
BMI	26 ± 3.7	27 ± 3.8	0.33
Enrolment diagnosis			0.37
Stable angina	42 (33%)	50 (41%)	
Unstable angina	68 (53%)	60 (50%)	
Acute MI	18 (14%)	10 (8%)	
Shock	0 (0%)	1 (1%)	
Procedural characteristics			
Revascularisation territory			
LAD	39 (49%)	37 (33%)	0.40
LCX	67 (53%)	54 (49%)	0.53
RCA	39 (31%)	38 (34%)	0.56
Native vessels treated			
LAD	14 (11%)	16 (13%)	0.70
LCX	13 (10%)	15 (12%)	0.43
RCA	16 (13%)	22 (18%)	0.38
LM	3 (2.3%)	2 (1.6%)	1.00
Disease complexity			
Three-vessel disease	24 (19%)	44 (36%)	<0.01
Multiple grafts treated	4 (3.2%)	3 (2.6%)	1*
In stent restenosis	10 (8%)	10 (8%)	0.91
Number of stents per lesion	2 [1–2][a]	2 [1–3][a]	0.21
Total stent length, mm	26 [18–40][a]	32 [18–57][a]	0.02
Average stent diameter, mm	3.7 ± 0.6	3.2 ± 0.7	<0.001
Success rate			
Angiographic success	124 (97%)	117 (98%)	0.46
Number of lesions successfully treated	1 [1–2][a]	1 [1–2][a]	0.97
Distal protection device used	6 (4.7%)	2 (1.6%)	0.28
Glycoprotein IIb/IIIa inhibitors	53 (41%)	26 (21%)	<0.01

BMI, body mass index; BMS, bare-metal stent; CAD, coronary artery disease; DES, drug-eluting stent; IQR, interquartile range; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; MI, myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standard deviation.

*P-value by Fisher's exact test.

[a]Data presented as median [interquartile range].

we had to restrict the number of possible confounders entered into the model [25]. Separate Cox regression analyses were performed to identify independent predictors of adverse events using all clinical and procedural variables listed in Tables I and II. These independent predictors are shown in the results section and were entered into the Cox regression model to obtain the adjusted hazard ratios (HR) and 95% confidence intervals (CI). All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL).

RESULTS

Survival status was available for 98.4% of the BMS patients and 99.4% of the DES patients. Clinical follow-up consisted of 1,582 person-years. The baseline and procedural characteristics of patients in both groups are depicted in Table I. Overall both groups were very similar; however, patients in the DES group were less likely to have hyperlipidaemia or a family history of coronary artery disease. Further, procedural characteristics differed in terms of a higher frequency of three-vessel

disease, a smaller average stent diameter and a longer total stented length in the DES group. The use of glycoprotein IIb/IIIa inhibitors decreased over time, from 41% in the BMS group to 21% in the DES group ($P = 0.001$). Whereas, the duration of post-discharge clopidogrel increased from a median of three (IQR 2–6) in the BMS group to 6 months (IQR 6-6; $P < 0.001$) in the DES group. In univariate analysis, the prescribed duration of clopidogrel was not significantly related to TVR (P-value $= 0.15$) or any of the other clinical outcomes. No differences in self-reported long-term medications were observed (Table II).

Event rates are depicted in Table III. At 87 months (7.25 years), a total of 101 patients died. Cause of death was cardiac in 66% in the BMS group and 70% in the DES group. Cumulative all-cause mortality was 46% vs. 42% in the BMS and DES groups, respectively (Fig. 1). When adjusting for independent predictors there was no significant improvement in cumulative mortality. Independent predictors (P-value < 0.1) of both cardiac and all-cause mortality at 7.25 years were increasing age, diabetes mellitus, renal impairment, enrolment diagnosis, and the left anterior descending (LAD) as revascularization territory.

The cumulative incidence of the combined endpoint mortality or MI was 57% in the BMS group vs. 60% in the DES group (Fig. 2). Independent predictors (P-value < 0.1) of mortality or MI at 7.25 years were diabetes mellitus, renal impairment, and enrolment diagnosis.

At 7.25 year, cumulative TVR was 41% in the BMS group as compared to 29% in the DES group (Fig. 3). In the DES group TVR was reduced by 37% (adjusted HR 0.63, 95% CI: 0.39–1.0). Two separate TVRs in the BMS group and one TVR in the DES group that were performed due to angiographic follow-up are not considered as an event. A total of six (5.0%) patients treated with BMS suffered from stent thrombosis occurring at a median of 220 days (IQR 163–1,198) versus only one (0.8%) in the DES group occurring at 606 days. The only independent predictor (P-value < 0.1) of TVR at 7.25 years was previous MI.

Cumulative MACE in the BMS group was 73% vs. 68% in the DES group (Fig. 4). Independent predictors (P-value < 0.1) of MACE at 7.25 years were increasing age, enrolment diagnosis and, average stent diameter.

TABLE II. Self-Reported Medical Treatment at 3-Year Follow According to Stent Type

Alive at 3 years	BMS ($n = 99$)	DES ($n = 99$)	P-value
Aspirin	85 (86%)	81 (82%)	0.44
Anticoagulants	17 (17%)	22 (22%)	0.37
β-blockers	81 (82%)	83 (84%)	0.71
ACE inhibitors or AT1 antagonists	54 (55%)	56 (57%)	0.78
Diuretics	31 (31%)	30 (30%)	0.88
Statins	93 (94%)	93 (94%)	1.0

ACE, angiotensin converting enzyme; AT1, angiotensin II type 1 receptor; BMS, bare-metal stent; DES, drug-eluting stent.

DISCUSSION

The present study shows that the unrestricted use of DES in SVG remains safe and effective as compared to BMS up to 7 years of follow up, illustrated by similar mortality rates and clinically relevant lower rates of TVR in patients treated with DES.

TABLE III. Association Between Stent Type Used and Event Rates: At 30 days and At 7.25 Years

	Number of events (Kaplan–Meier estimate)		Observed HR (95% CI)	Adjusted HR (95% CI)
	BMS ($n = 126$)	DES ($n = 121$)	DES vs. BMS	DES vs. BMS
Events at 30 days after PCI				
Total mortality	7 (5.6%)	4 (3.3%)		
Cardiac mortality	6 (4.8%)	4 (3.3%)		
Mortality or myocardial infarction	10 (7.9%)	7 (5.8%)		
Target vessel revascularization	4 (3.2%)	2 (1.7%)		
Major adverse cardiac events	14 (11%)	8 (6.6%)		
Events at 7.25 years after PCI				
Total mortality	58 (46%)	43 (42%)	0.84 (0.56–1.3)	0.90 (0.59–1.4)[a]
Cardiac mortality	38 (35%)	30 (33%)	0.90 (0.55–1.4)	0.93 (0.56–1.5)[a]
Mortality or myocardial infarction	72 (57%)	63 (60%)	1.0 (0.74–1.5)	0.97 (0.71–1.4)[b]
Target vessel revascularisation	45 (41%)	28 (29%)	0.62 (0.38–0.99)*	0.63 (0.39–1.0)[c]
Major adverse cardiac events	92 (73%)	74 (68%)	0.81 (0.59–1.1)	0.93 (0.67–1.3)[d]

HR, Hazard ratio; CI, confidence interval; BMS, bare-metal stent; DES, drug-eluting stent; BMI, body mass index, PCI, percutaneous coronary intervention.

The observed (unadjusted) and adjusted HR compares DES vs. BMS with BMS as the reference.

*P-value < 0.05.

[a-b]Adjusted for independent predictors of the outcome of interest as described in the results section.

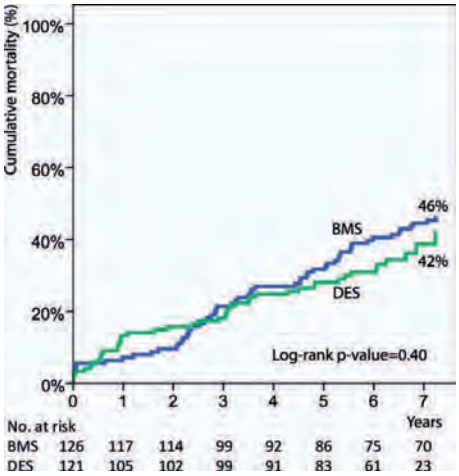

Fig. 1. Kaplan–Meier curve of cumulative mortality. BMS, bare-metal stent; DES, drug-eluting stent. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary. com.]

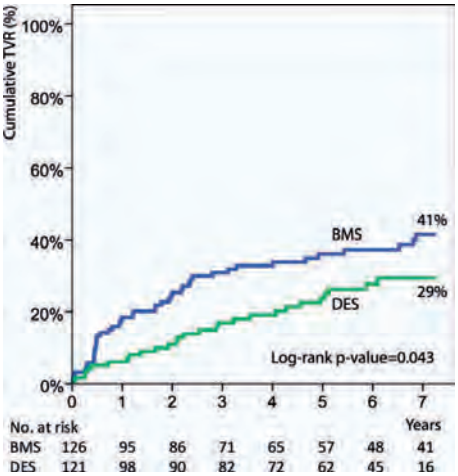

Fig. 3. Kaplan–Meier curve of cumulative TVR. BMS, bare-metal stent; DES, drug-eluting stent; TVR, target vessel revascularization. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

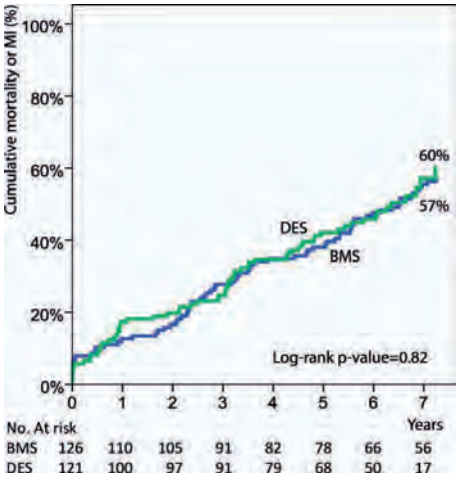

Fig. 2. Kaplan–Meier curve of cumulative mortality or MI. BMS, bare-metal stent; DES, drug-eluting stent; MI, myocardial infarction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

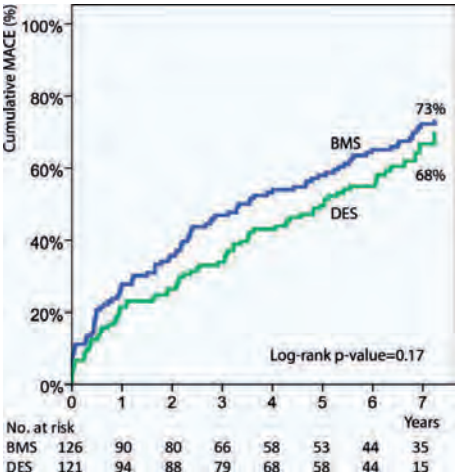

Fig. 4. Kaplan–Meier curve of cumulative MACE. BMS, bare-metal stent; DES, drug-eluting stent; MACE, major adverse cardiac event (combined endpoint of all-cause mortality, myocardial infarction, and target vessel revascularization). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

We have already reported the 4-year follow up of DES vs. BMS in SVG [23]. At four years DES was considered safe and effective, illustrated by lower rates of TVR. These results have been validated by a meta-analysis of three randomized controlled trials—although the maximum follow-up duration in the three trials was 2.5 years [17].

The treatment of SVG disease represents about 3–8% of the PCI cases in our centre. Atherosclerotic disease in SVG has several peculiarities which account for the poor outcome compared to native coronary arteries, including a different plaque composition, higher plaque burden, more friable material and frequent superimposed thrombus [9,10]. Further, the restenotic process in SVGs is different with several distinct phenomena including intimal hyperplasia, progression of atherosclerosis, local inflammatory reaction, and thrombosis [12] whilst the major process in the coronaries is intimal hyperplasia [11]. Therefore, regarding clinical outcomes, it is unclear whether results in native coronary arteries, that is improved outcomes with use of DES, would also hold for SVG.

The present study included a total of 250 "real world" consecutive patients treated for SVG disease. In terms of absolute reduction, at 7.25 years we find a reduction in TVR of 12%, which is identical to the absolute reduction in TVR at 1 year. The present study underscores the sustained clinical benefit with DES in SVG over BMS over 7.25 years.

Further, the absolute risk reduction, representing the number needed to treat (NNT), is very comparable—if not equal—to studies in patients with single de novo lesions (12% absolute TVR reduction at 7.25 years in the present study, 16% at 5 year in the RAVEL study, [26] 11% at 5 year in the SIRIUS study, [27] and 10% at 5 year in the TAXUS study [28]).

In the present study the overall event rates remain high as compared to event rates after native vessel stenting [29]. Overall morality at 7.25 years is 43%. The most likely explanation for the high event rates is the relatively high mean age, the high frequency of measured comorbidities and risk factors, and the fact that all patients in the present study presented with an occlusion in a SVG.

To date, other large-scale registries have not yet reported long-term outcome (>3 years) in this specific patient subset [18,30,31]. Therefore the duration of the follow-up of the present study is probably the longer worldwide and the institution has a unique reputation for long-term follow-up [32]. Interestingly, the long term cumulative incidence of MACE of 73% in BMS patients at 7.25 years is identical to the cumulative incidence of MACE in Dutch patients at 5 years treated two decades ago with balloon angioplasty [33]. This suggests that the expected survival free of MACE increased with 27 months (2.25 years) between patients treated for SVG lesions in 1985 and in 2002. Today, with the use of DES the estimated cumulative incidence of MACE further improved to 68% at 7.25 years.

Of note, the study population stems from an era when embolic protection devices were not yet fully established. Embolic protection devices were used in less than 5% of cases. Embolic protection devices have been shown to reduce MACE by up to 40% [34]. As such the use of embolic protection devices in SVG PCI is a class I level of recommendation B recommendation in the recent ESC/EACTS guidelines on myocardial revascularisation [35]. The implementation of embolic protection devices could have had a positive impact on absolute numbers of short and longer-term outcome in our study cohort.

A limitation of the present study is that the results are based on a nonrandomized patient population without completely identical groups. In the DES group, more complex patients were being treated with PCI compared to the BMS group. Although we statistically adjusted for clinical and procedural differences between both groups, it could be debated whether this is sufficient. Further, the results are based on a relatively small patient cohort and therefore may have lack of power. Large-scale randomized controlled trials with long-term follow-up are advocated to prove the long-term benefit of DES over BMS in SVG.

CONCLUSIONS

In the present study, the use of DES for SVG lesions appeared safe and effective up to 7.25 years, and DES resulted in a clinically relevantly lower rate of TVR.

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6.3

The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy.

Farooq V, Girasis C, Magro M, Onuma Y, Morel MA, Heo JH, Garcia-Garcia H, Kappetein AP, van den Brand M, Holmes DR, Mack M, Feldman T, Colombo A, Ståhle E, James S, Carrié D, Fournial G, van Es GA, Dawkins KD, Mohr FW, Morice MC, Serruys PW.

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The CABG SYNTAX Score - an angiographic tool to grade the complexity of coronary disease following coronary artery bypass graft surgery: from the SYNTAX Left Main Angiographic (SYNTAX-LE MANS) substudy

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The references and also the accompanying supplementary data can be found in the online version of this paper at the following website: www.eurointervention.org

KEYWORDS

- CABG
- PCI
- SYNTAX Score
- CABG SYNTAX Score
- Leaman score

Abstract

Aims: The SYNTAX Score (SXscore) has established itself as an important prognostic tool in patients undergoing percutaneous coronary intervention (PCI). A limitation of the SXscore is the inability to differentiate outcomes in patients who have undergone prior coronary artery bypass graft (CABG) surgery. The CABG SXscore was devised to address this limitation.

Methods and results: In the SYNTAX-LE MANS substudy 115 patients with unprotected left main coronary artery disease (isolated or associated with one, two or three-vessel disease) treated with CABG were prospectively assigned to undergo a 15-month coronary angiogram. An independent core laboratory analysed the baseline SXscore prior to CABG. The 15-month CABG SXscore was calculated by a panel of three interventional cardiologists. The CABG SXscore was calculated by determining the standard SXscore in the "native" coronary vessels ("native SXscore") and deducting points based on the importance of the diseased coronary artery segment (Leaman score) that have a functioning bypass graft anastomosed distally. Points relating to intrinsic coronary disease, such as bifurcation disease or calcification, remain unaltered. The mean 15-month CABG SXscore was significantly lower compared to the mean baseline SXscore (baseline SXscore 31.6, SD 13.1; 15-month CABG SXscore 21.2, SD 11.1; p<0.001). Reproducibility analyses (kappa [k] statistics) indicated a substantial agreement between CABG SXscore measurements (k=0.70; 95% CI [0.50-0.90], p<0.001), with the points deducted to calculate the CABG SXscore the most reproducible measurement (k=0.74; 95% CI [0.53-0.95], p<0.001). Despite the limited power of the study, four-year outcome data (Kaplan-Meier curves) demonstrated a trend towards reduced all-cause death (9.1% vs. 1.8%, p=0.084) and death/CVA/MI (16.4% vs. 7.0%, p=0.126) in the low compared to the high CABG SXscore group.

Conclusions: In this pilot study the calculation of the CABG SXscore appeared feasible, reproducible and may have a long-term prognostic role in patients with complex coronary disease undergoing surgical revascularisation. Validation of this new scoring methodology is required.

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Introduction

The SYNTAX Score (SXscore) (http://www.syntaxscore.com)[1-5] has established itself as an important prognostic tool in risk stratifying patients being considered for revascularisation, and has been validated in patients undergoing percutaneous coronary intervention (PCI) at one-year follow-up[6-11]. In addition, the SXscore has been applied to contemporary drug-eluting stent trials enrolling "all-comers" type populations, and has been shown to be an independent predictor of one-year mortality and major adverse cardiac events (MACE)[12-14].

As a consequence, the SXscore is now advocated in both the European and the US revascularisation guidelines in aiding the risk stratification of patients with complex coronary artery disease to the most appropriate revascularisation modality[15-17]. Furthermore, the US FDA (Food and Drug Administration) recommends the application of the SXscore in selecting low-intermediate SXscore patients with unprotected left main coronary artery disease in the ongoing EXCEL Trial (ClinicalTrials.gov Identifier: NCT01205776), and low SXscore patients suitable for transcatheter aortic valve implantation in the SURTAVI Trial (ClinicalTrials.gov Identifier: NCT01586910). However, a limitation of the SXscore is the inability to apply it usefully to patients who have previously undergone CABG.

Based on the principles first defined by Leaman et al (Leaman score)[18], the SXscore takes into account both the coronary anatomy and also the importance of the diseased coronary artery segment supplying the myocardium – termed "vessel-segment weighting". Although the baseline SXscore, calculated prior to surgical revascularisation, has been shown not to have any effect on the short to long-term prognosis after CABG[3,4,7,19,20], it was hypothesised that a suitably developed CABG SXscore that takes into account native coronary disease anatomy, including features such as calcification, bifurcation disease and the effects of surgical revascularisation on the vessel-segment weighting, may have potential clinical and research applications. The purpose of this pilot study is to examine the feasibility of the newly developed CABG SXscore in the SYNTAX-LE MANS angiographic substudy[21].

Methods

The overall study design of the all-comers SYNTAX Trial[3,5,22] and the SYNTAX-LE MANS substudy[21] have previously been described. In brief, SYNTAX-LE MANS was a predefined substudy of patients from the randomised SYNTAX Trial who provided a separate written, informed consent for the substudy entry[21]. Eligible patients were those with left main disease (isolated or associated with one, two or three-vessel disease) who did not have renal dysfunction (defined as creatinine >2.0 mg/dL [150 µmol/L]) or hypersensitivity to contrast agents that could not be adequately premedicated. Per protocol, the time window for the 15-month angiogram was set between 14 and 16 months post-allocation. Patients enrolled in the study who had a clinically driven angiogram from 9 to 13 months (inclusive) after treatment allocation were permitted to use the earlier coronary angiogram to fulfil the 15-month angiographic requirement.

CABG SYNTAX SCORE ANALYSIS

Baseline and 15-month coronary angiograms were analysed side by side by a panel of three interventional cardiologists to calculate the 15-month CABG SXscore. All reviewers were blinded to the clinical outcomes of the patient analyses and to the baseline SXscore, undertaken prior to CABG by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) as part of the original SYNTAX Trial[3].

The CABG SXscore calculation was repeated on 30 randomly selected cases at a three-month interval with the reviewers blinded to the original baseline and CABG SXscores. Intraobserver reproducibility analyses were undertaken.

CABG SYNTAX SCORE

The CABG SXscore is essentially the SXscore of the "native" coronary vessels ("native SXscore"), with points deducted based on the vessel-segment weighting of the bypassed coronary vessel as previously proposed by Leaman et al[18].

SYNTAX SCORE

In brief, the SXscore[1-4] was developed by combining the importance of a diseased coronary artery segment by the vessel-segment weighting (Leaman score)[18], adverse characteristics of such a lesion for revascularisation (ACC/AHA lesion classification)[23,24] and the Medina classification system for bifurcation lesions[25]. Each vessel segment, 1.5 mm in diameter or greater (**Figure 1**, labelled 1 to 16), with a ≥50% diameter stenosis by visual estimation, is awarded a multiplication factor related to coronary lesion location and severity **(Figure 2)**. Further characterisation of the coronary lesions leads to the addition of more points, which includes features of total occlusions (duration, length, blunt stump, presence of bridging collaterals or side branch), presence of bifurcation (based on the Medina classification) or trifurcation disease (number of diseased branches involved), side branch angulation, aorto-ostial lesion, severe tortuosity, lesion length >20 mm, heavy calcification, thrombus and diffuse or small vessel disease. An online SXscore algorithm[1] automatically summates each of these features to calculate the final total SXscore.

LEAMAN SCORE

The Leaman score is based on the severity of luminal diameter narrowing, and is weighted according to the usual blood flow to the left ventricle (LV) in each vessel or vessel segment based on whether the coronary system is right or left dominant[18].

In a right dominant system the right coronary artery (RCA) supplies approximately 16% and the left coronary artery (LCA) approximately 84% of the blood flow to the LV. This 84% is normally directed 66% to the left anterior descending (LAD) and 33% to the left circumflex (LCx) vessels. Thus the LAD and LCx respectively carry approximately 3.5 times and 1.5 times as much blood as the RCA. In a left dominant system the LV receives all of its blood supply from the LCA; consequently, the RCA is not weighted and its value is assigned to the LCA, thereby leading to a heavier vessel-segment weighting of the LAD and LCx compared to a right dominant system[18,26-28]. These principles ultimately formed the basis of

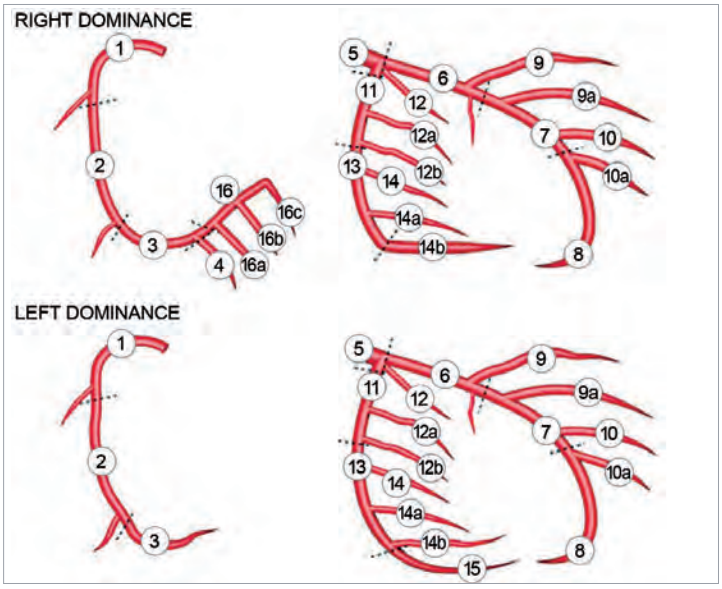

Figure 1. *The effect of right and left arterial dominance on the segment numbering – refer to Table 1 for the segment-weighting for the respective arterial segments. Anatomical description of the segment numbers has previously been described[2] and is included in the supplementary appendix.*

the segment-weighting factors that were incorporated into the SXscore **(Table 1)**[1-4].

CALCULATION OF THE CABG SYNTAX SCORE

In order to allow consistency and reproducibility in the application of the CABG SXscore, five rules were adhered to in calculating the CABG SXscore.

1. The SXscore of the native coronary vessels (native SXscore) was analysed using the standard methodology (http://www.syntaxscore.com)[1], utilising the bypass graft angiogram as necessary to allow visualisation of the entire vessel.
2. All the bypass grafts were analysed to establish the vessel-segment weighting of the "protection" conferred by the bypass grafts **(Figure 1, Table 1)**.
3. Based on the presence of obstructive or non-obstructive bypass disease by visual assessment, segment-weighting points were deducted from the native SXscore:
   a. Patent bypass graft to a significant coronary lesion: segment-weighting points for the coronary lesion were deducted, provided there was no intervening significant coronary disease **(Figure 3)**.

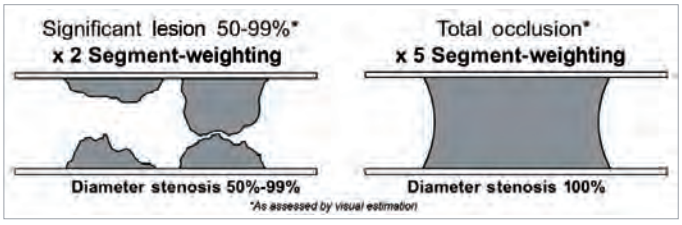

Figure 2. *Segment-weighting multiplication factors utilised in the SYNTAX Score – used to calculate the points required to deduct from the "native SXscore" to calculate the CABG SYNTAX Score.*

Table 1. Coronary vessel segment-weighting based on the principles first established by Leaman et al[18] and incorporated into the SYNTAX Score[2]. Refer to Figure 1 for location of segment numbers on the coronary tree based on arterial dominance.

Segment number	Right dominance	Left dominance
1 (RCA proximal)	1	0
2 (RCA mid)	1	0
3 (RCA distal)	1	0
4 (Posterior descending artery)	1	n/a
16 (Posterolateral branch from RCA)	0.5	n/a
16a (Posterolateral branch from RCA)	0.5	n/a
16b (Posterolateral branch from RCA)	0.5	n/a
16c (Posterolateral branch from RCA)	0.5	n/a
5 (Left main)	5	6
6 (LAD proximal)	3.5	3.5
7 (LAD mild)	2.5	2.5
8 (LAD apical)	1	1
9 (First diagonal)	1	1
9a (First diagonal)	1	1
10 (Second diagonal)	0.5	0.5
10a (Second diagonal)	0.5	0.5
11 (Proximal circumflex artery)	1.5	2.5
12 (Intermediate/anterolateral artery)	1	1
12a (Obtuse marginal)	1	1
12b (Obtuse marginal)	1	1
13 (Distal circumflex artery)	0.5	1.5
14 (Left posterolateral)	0.5	1
14a (Left posterolateral)	0.5	1
14b (Left posterolateral)	0.5	1
15 (Posterior descending artery)	n/a	1

RCA: right coronary artery; LAD: left anterior descending artery; n/a: not applicable

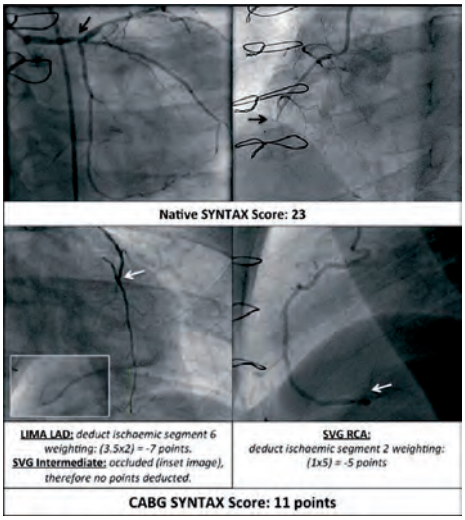

Figure 3. *Example of the calculation of the CABG SXscore in a patient with distal left main trifurcation disease and an occluded mid RCA. The native SXscore was 23 (upper images). A patent LIMA to the LAD with no intervening obstructive coronary disease (lower left image) led to the deduction of 3.5×2 points (x2 segment-weighting due to ischaemic LAD) from the native SXscore. An occluded SVG to the intermediate led to no points being deducted (inset lower left image). A patent SVG to the distal RCA led to 1×5 points (x5 segment-weighting due to occluded mid RCA) deducted from the native SXscore. Final CABG SXscore was therefore 23-7-5=11 points. LIMA: left internal mammary artery; SVG: saphenous vein graft; RCA: right coronary artery. Black arrows indicate obstructive native coronary disease; white arrows indicate patent anastomosis sites of grafts to vessels*

b. Occluded bypass graft: native SXscore remained unaltered **(Figure 3)**.

c. Bypass graft with obstructive (50-99%) disease **(Figure 4)**:

i. obstructive native coronary lesion (50-99%): no segment-weighting points deducted;

ii. occluded native coronary lesion (100%, TIMI 0 flow): x3 segment-weighting points deducted.

With an obstructive native coronary lesion (50-99%), it is assumed that a significantly diseased graft (50-99%) would confer no additional benefit to the blood supply to the affected coronary vessel; consequently, there would be no net gain or loss in the segment-weighting points to the native SXscore. Conversely, if the coronary vessel was occluded, then a diseased graft (50-99%) would provide "ischaemic protection" to the territory supplied by the occluded lesion. Consequently, the segment-weighting factor would be reduced from x5 (occluded vessel) to x2 (non-occluded vessel with a significant lesion [50-99%]), i.e., a deduction of x3 segment-weighting factor from the native SXscore.

4. Any further native coronary disease clearly identified through the angiograms of the bypass grafts were added to the native SXscore. Lesions ≥3 reference vessel diameters were viewed as two separate lesions and within this distance as one lesion.

5. If an obstructive coronary lesion interferes with the blood flow to the vessel being protected by the bypass graft, then the points deducted were for the segment weighting of the lesion only **(Figure 5)**.

Points related to the lesion characteristics of the "native" coronary disease, such as calcification, bifurcation disease, total occlusion, etc., would remain unaltered as these reflect the native coronary anatomy. Further detail on the SXscore/Leaman score and applications of the CABG SXscore are provided in the Supplementary Appendix.

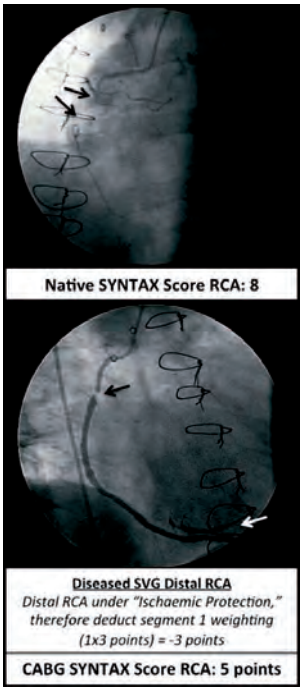

Figure 4. *Principle of "ischaemic protection" in the CABG SXscore. Upper image: occluded mid RCA (segment 2 - black arrows) with bridging collaterals: native SXscore for the RCA is 8. Lower image: SVG anastomosed to distal RCA (white arrow). If the SVG was free of obstructive disease then the CABG SXscore would be 8 minus (1×5)=3 points. If the SVG was diseased with an obstructive lesion as illustrated (lower image, black arrow) the distal RCA would be under "ischaemic protection". Consequently x2 weighting factor for the RCA should remain – therefore x3 weighting needs to be deducted leading to a CABG SXscore of 8 minus (1×3) points=5 points. If the SVG was occluded then the CABG SXscore would remain unaltered at 8 points. RCA: right coronary artery; SVG: saphenous vein graft*

STATISTICAL ANALYSIS

Continuous variables are expressed as means±SD. Comparisons of means and four-year outcomes (Kaplan-Meier curves) were performed with the paired t-test and log-rank test respectively. Intraobserver variability (tertile partitioning) was determined with kappa statistics (<0 none, 0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, 0.81-1.00 almost perfect) on the native SXscore, deducted points and CABG SXscore[4]. A two-sided p-value <0.05 was considered significant for all tests. Analyses were conducted with SAS System Software Version 8.0+ (SAS Institute, Cary, NC, USA) and SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

In total, 271 patients were enrolled in the SYNTAX-LE MANS study, 115 of whom were enrolled in the CABG arm. Available 15-month coronary angiograms were suitable for analysis in 113 of 115 (97.4%) CABG patients. No patients died in the CABG arm from baseline to undergoing the 15-month coronary angiogram. One patient had no angiographic films available and a further patient did not have native coronary vessels filmed. Baseline characteristics for the SYNTAX-LE MANS substudy have been published previously[21].

COMPARISONS OF THE BASELINE SYNTAX SCORE AND 15-MONTH CABG SYNTAX SCORE

Comparisons of the baseline SXscores and 15-month CABG SXscores demonstrated a significant decline in the mean value of the 15-month CABG SXscores **(Figure 6)**. Both the baseline SXscore and the 15-month CABG SXscore appeared to be broadly normally distributed with the mean 15-month CABG SXscore significantly moved to the left **(Figure 7)**. The mean 15-month CABG SXscore was significantly lower compared to the mean baseline SXscore (baseline SXscore 31.6, SD 13.1; 15-month CABG SXscore 21.2, SD 11.1; p<0.001) **(Figure 7)**.

Comparisons of the baseline SXscore and 15-month native SXscore did not demonstrate any significant statistical differences (baseline SXscore 31.6, SD 13.1; 15-month native SXscore 31.1, SD 12.2; p=0.50). The mean number of points deducted from the 15-month native SXscore to derive the CABG SXscore was 9.9 (SD 5.3) **(Figure 8)**.

REPRODUCIBILITY ANALYSES

The intraobserver variability for the 15-month native SXscore (k=0.70; 95% CI: 0.50-0.91, p<0.001), points deducted from the native SXscore to derive the 15-month CABG SXscore (k=0.74; 95% CI: 0.53-0.95, p<0.001) and the final 15-month CABG SXscore (k=0.70; 95% CI: 0.50-0.90, p<0.001) were all substantial. The number of points deducted to derive the 15-month CABG SXscore was the most reproducible measurement.

CLINICAL OUTCOMES

Due to limited power the present outcome analyses should be interpreted as exploratory and hypothesis-generating. The CABG SXscores were separated into two groups, divided by the median of the normally distributed 15-month CABG SXscores into low (0-21) (n=58) and high-risk groups (≥22) (n=55).

Four-year clinical outcome data demonstrated a trend towards an increased mortality in the high CABG SXscore group compared to the low CABG SXscore group (low CABG SXscore: 1.8%, high CABG SXscore: 9.1%, p=0.084) **(Figure 9)**. Furthermore, an increase in the composite of all-cause death/cerebrovascular accident (CVA)/ myocardial infarction (MI) at four years was also evident in the high CABG SXscore group compared to the low CABG SXscore group (low CABG SXscore: 7.0%, high CABG SXscore: 16.4%, p=0.126).

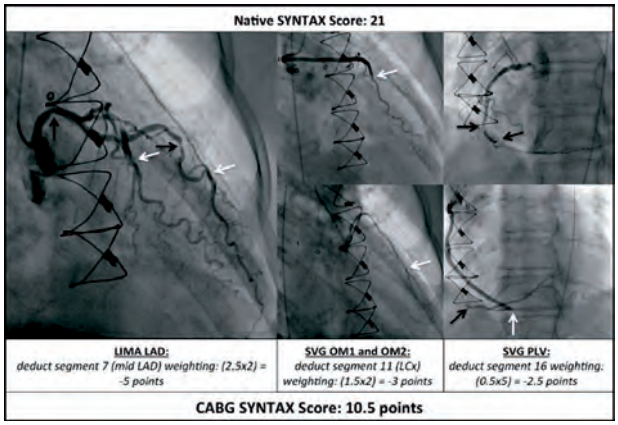

Figure 5. *Example of the calculation of the CABG SXscore in a patient with mid left main and two-vessel coronary disease. Native SXscore was 21. A patent LIMA anastomosed to the mid LAD, with upstream native mid LAD disease, and led to the segment-weighting (2.5×2 points) of the mid LAD (segment 7) being deducted from the native SXscore (left image). The LCx was protected by two OM SVGs leading to a deduction of 1.5×2 points from the native SXscore (middle image). The occluded PLV was protected by an SVG leading to the deduction of 0.5×5 points from the native SXscore (right image). Final CABG SXscore was therefore 21-5-3-2.5=10.5 points. LAD: left anterior descending artery; LCx: left circumflex; OM: obtuse marginal; RCA: right coronary artery; PLV: posterior left ventricular branch of the RCA; LIMA: left internal mammary artery; SVG saphenous vein graft. Black arrows indicate obstructive native coronary disease; white arrows indicate patent anastomosis sites of grafts to vessels.*

Notably, the Kaplan-Meier curves for all clinical outcomes in the low and high CABG SXscores did not start to separate until after one year of follow-up, with continued separation of the curves up to four years of follow-up. A peak in the incidence of all-cause

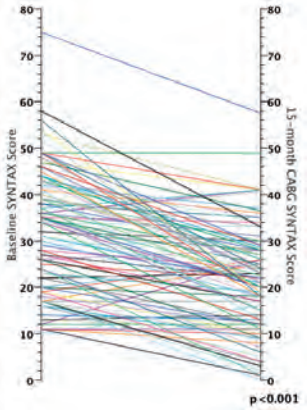

Figure 6. *Reduction in the CABG SYNTAX Score at scheduled coronary angiography at 15 months, compared to the baseline SYNTAX Score (n=113).*

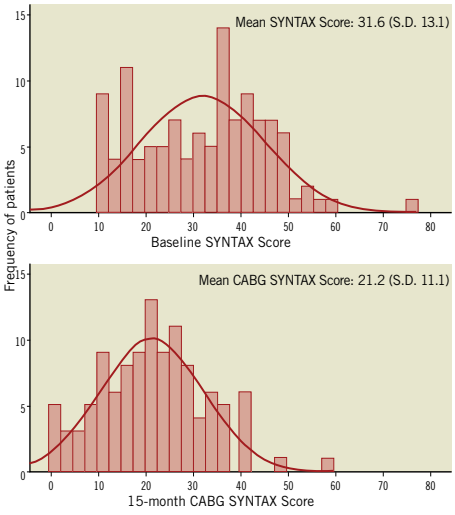

Figure 7. *Distribution of the baseline SYNTAX Scores and the 15-month CABG SYNTAX Scores (n=113). Note the significant decrease in the mean CABG SYNTAX Score compared to the mean baseline SYNTAX Score (p<0.001). SD: standard deviation.*

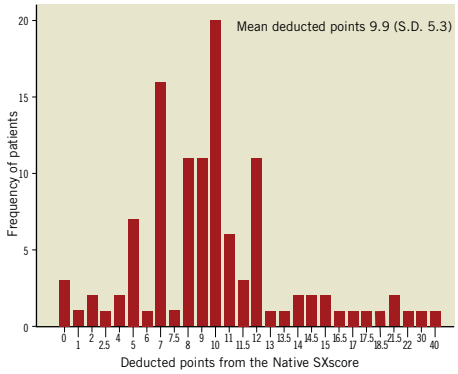

Figure 8. *Distribution of the deducted points from the native SXscore to calculate the CABG SXscore (n=113). SD: standard deviation.*

revascularisation was observed at approximately 15 months secondary to the scheduled study coronary angiogram triggering repeat revascularisation **(Figure 9)**.

Discussion

The main findings of this pilot study are: 1) that the application of the newly developed CABG SXscore appears feasible; 2) that the 15-month CABG SXscore demonstrated a significant decrease in value compared to the baseline SXscore (prior to CABG), secondary to a deduction in points attributed to the segment-weighting of the revascularised coronary vessels; 3) that the CABG SXscore appears to be a reproducible technique when performed by a panel of interventional cardiologists experienced in the reporting of the SXscore; 4) that the deduction of the segment-weighting related points due to the presence of bypass grafts was the most reproducible technique; and 5) that the CABG SXscore may have a long-term prognostic role. Further validation of this newly developed score is required.

The findings from this present study are consistent with the methodology adopted by Leaman et al when applying the Leaman score to patients pre and post CABG[18], namely that the segment-weighting for the treated vessel would be deducted if it had a functioning bypass graft anastomosed distal to the treated lesion. In comparison to the baseline SXscore, a clear and significant reduction in the 15-month CABG SXscore was evident. The main difference between the CABG SXscore and the Leaman score was that the points relating to lesion characteristics in the CABG SXscore remained.

One of the unavoidable limitations of the present study was that the coronary angiograms were taken 15 months post CABG and the results compared to the baseline SXscore taken prior to surgery. The mean baseline SXscore and the 15-month native SXscore did however not differ significantly (baseline SXscore 31.6, SD 13.1; 15-month native SXscore 31.1, SD 12.2; p=0.50), making the potential effects of native coronary disease progression at 15 months likely to be of lesser significance.

Conversely, as reported in the SYNTAX-LE MANS substudy, over a quarter of the CABG patients (27.2%) had a significantly diseased (≥50% to <100%) or obstructed (100%) bypass graft at 15 months[21]. These findings may have led to the underestimation of the 15-month CABG SXscore compared to if the CABG SXscore had been performed post CABG surgery. Although it has previously been reported that early bypass graft occlusion rates may be associated

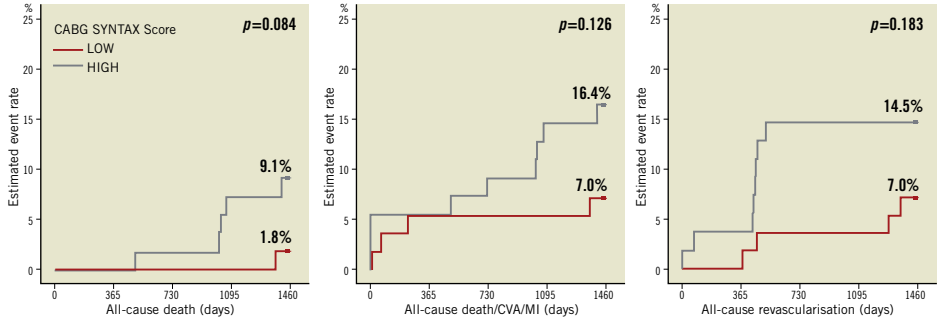

Figure 9. *Clinical outcomes separated by the median of the CABG SYNTAX Score into low (0-21) (n=58) and high (≥22) (n=55) score groups. A non-significant trend towards higher mortality (left image) and all-cause death/CVA/MI (middle image) were evident in the high CABG SYNTAX Score group at four years. The peak in repeat all-cause revascularisation between years one and two (right image) were secondary to patients undergoing scheduled coronary angiography, the findings of which triggered repeat revascularisation. CVA: cerebrovascular accident; MI: myocardial infarction*

with adverse clinical events[29-31], the reported loss of the bypass grafts in SYNTAX-LE MANS were not significantly associated with early MACCE[21].

It may be speculated that a proportion of these bypass grafts may potentially have been unnecessary. Early bypass graft patency rates for functionally significant native coronary lesions have been shown to be significantly higher compared to those for bypass grafts with functionally insignificant native coronary lesions[32-34]. Furthermore, angiographically defined percentage diameter stenoses or the minimum lumen diameter of native coronary vessels[29,35] and grafts that have competitive filling with the treated native vessel[36,37] have been shown to be predictors of insufficient flow and/or early graft failure. Consequently, despite the limitations, the 15-month CABG SXscore may potentially be representative of patients who have been surgically revascularised at baseline.

ASSOCIATION OF THE CABG SYNTAX SCORE WITH CLINICAL OUTCOMES

The SXscore taken prior to surgery has consistently been shown not to have any significant effect on the short to long-term prognosis after CABG[2-4,7,19,20]. It has previously been suggested that this observation may be related to the fact that bypass grafts are anastomosed distal to the proximal disease regardless of the complexity of the native coronary disease, providing there are suitable graftable targets[4,38]. With the CABG SXscore this concept is potentially challenged, with the observation of a non-significant trend towards a higher longer-term mortality and death/MI/CVA in the high (compared to the low) CABG SXscore group. MACCE was not examined as the 15-month scheduled coronary angiogram triggered repeat revascularisation **(Figure 9)**.

PREVIOUS STUDIES

Alderman et al[39] previously demonstrated in The Bypass Angioplasty Revascularisation Investigation (BARI) trial – consisting of patients treated with percutaneous or surgical revascularisation who underwent entry and five-year coronary angiographic follow-up – that native coronary disease progression (and not the extent of initial revascularisation) was the predominant determinant of the recurrence of angina and jeopardised myocardium at five years. Notably within the BARI Trial two thirds of the increase in myocardial jeopardy at five years was in previously untreated coronary vessels.

Although other studies have suggested that incomplete surgical revascularisation may be associated with short and long-term adverse outcomes[40,41], further predominantly more contemporary studies have suggested that "reasonable" incomplete surgical revascularisation does not have an adverse effect on long-term clinical outcomes[42-45]. Furthermore, the long-term survival of patients treated with surgical revascularisation in the CASS (Coronary Artery Surgery Study)[46] and Rotterdam[47] registries has been shown to be associated with more extensive preoperative coronary disease, which in turn was linked to the higher prevalence and severity of other clinical risk factors.

In addition, the Duke graft index[48] – an anatomical-based scoring system for patients who had previously undergone CABG – was demonstrated to be significantly more associated with long-term prognosis compared to the native coronary anatomy prior to CABG. Remarkably, the Duke graft index had a design concept that in principle was similar to the CABG SXscore, namely associating anatomical coronary disease (Duke Graft index: based on the number of diseased coronary territories; CABG SXscore: a more sophisticated assessment of the coronary anatomy as previously described) with the level of protection to the diseased territories conferred by bypass grafts in both scores.

IMPLICATIONS OF THE CABG SYNTAX SCORE FOR CLINICAL PRACTICE

The CABG SXscore may thus be regarded as both a marker of anatomical coronary disease complexity, and of the degree of revascularisation secondary to the deduction of segment-weighting points related to the bypass grafts. Furthermore, it may be speculated that the CABG SXscore consisting of anatomical characteristics of the coronary vessel – such as bifurcation disease, calcification, total occlusions, etc. – may reflect the clinical risk profile of the patient and the likelihood of native coronary (and possibly non-coronary as detailed below) atherosclerotic disease progression which, importantly, may actually target the bypass grafts.

It has previously been suggested that the SXscore is a marker of patients with a more adverse clinical risk profile who have evidence of systemic atherosclerotic disease, and are thus at greater longer-term cardiovascular and cerebrovascular risk[19,20,49]. This hypothesis is supported by the significant and direct relationship of the 10-year predicted Framingham risk scores with the prevalence and magnitude of coronary artery calcium scores[50]. In addition, the ankle-brachial index[51-54] and common carotid intima-media thickness[55-58], both markers of extra-cardiac disease, have been correlated with the severity of coronary artery disease and even clinical events.

Notably, the clinical outcomes in the present study did not start to separate until after one year, and continued to separate at up to four years **(Figure 9)**. It may be further hypothesised that the curves would continue to separate in the longer term where the clinical manifestations of continued native atherosclerotic coronary disease progression, and importantly bypass graft disease progression particularly with SVG, would become more apparent. Consistent with these hypotheses are the findings that SVGs have been shown to be protective in the first seven years, and that thereafter mortality increases significantly in parallel to the gradual loss of SVG patency[47,59].

POTENTIAL CLINICAL AND RESEARCH APPLICATIONS OF THE CABG SYNTAX SCORE

Potential clinical applications of the CABG SXscore include long-term risk stratification of patients who have previously undergone CABG to aid in the identification of a group at high risk for future clinical events and repeat revascularisation. Even without the use of a CABG SXscore, it may be further postulated that higher SXscore

patients may benefit more from undergoing revascularisation with more durable grafts that have a proven long-term patency (e.g., LIMA and RIMA) compared to SVG[60,61].

Although aggressive risk factor control would undoubtedly improve the prognosis of all these patients, perhaps future study may target patients with a higher SXscore/CABG SXscore who may potentially benefit from more aggressive risk factor control with established and emerging drugs that cause atherosclerotic disease regression.

Other potential applications of the CABG SXscore in a research setting include the allowance of the incorporation of CABG patients into contemporary stent trials measuring the SXscore, where such patients are at present excluded.

STUDY LIMITATIONS

As previously discussed, apart from the time frame at which the CABG SXscore was taken, the main limitation of this study is that there was limited power to examine long-term clinical outcomes. Despite this limitation, a non-significant trend towards more adverse clinical outcomes in the higher CABG SXscore group was seen, which is further supported by the concept of the Duke graft index, as previously discussed[48].

One other limitation is that the CABG SXscore does not account for the type of graft anastomosed and the characteristics of the graft disease (if present), except if there is obstructive graft disease or not. This is perhaps more notable with the LIMA bypass graft given its proven higher long-term patency rates compared to other types of bypass graft[60,61]. The hypothesis central to the CABG SXscore does, however, relate to the native SXscore and its apparent association with clinical comorbidity, with the additional "protection" conferred by the bypass grafts. Furthermore, reducing the CABG SXscore by an arbitrary number of points based on the type and numerous anatomical complexities of the bypass graft would substantially increase the complexity of the analyses, making this impractical.

FUTURE DIRECTIONS

Potentially, the integration of the CABG SXscore into an online algorithm, as is currently available with the SXscore[1], may serve to simplify the calculation of the CABG SXscore. The functional SYNTAX Score – a fractional flow reserve (FFR) guided SYNTAX scoring methodology – has recently been demonstrated to improve the diagnostic accuracy of the SXscore[62]. Furthermore, the feasibility of undertaking non-invasive anatomical and fractional flow measurements has since been proven, utilising computational fluid dynamics applied to coronary computed tomography (CT) angiography[63]. The application of this emerging technology to the CABG SXscore may improve the diagnostic accuracy and reproducibility of the CABG SXscore. In addition, the non-invasive combined coronary CT and FFR technology may potentially allow for the automatic adjustment of the vessel-segment weighting for coronary vessels based on actual measured blood flow, in order to calculate a more "physiological" functional CABG SXscore.

Conclusion

The calculation of the CABG SXscore is feasible, reproducible and may have a long-term prognostic role in the assessment of risk in patients undergoing coronary artery bypass grafting. Confirmation and validation of the findings from this pilot study are required in larger studies.

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Conflict of interest statement

K.D. Dawkins is a full-time employee in Boston Scientific and holds stock in Boston Scientific. M. Mack has served on the Speakers' Bureau of Boston Scientific, Cordis and Medtronic. T. Feldman reported serving on the Speakers' Bureau of Boston Scientific, receiving grant support from Abbott, Atritech, BSC, Edwards, Evalve, and consulting for Abbott, Coherex, Intervalve, Square One, WL Gore. M. Morice reported that her institution received a research grant from Boston Scientific. M.A. Morel, M. van der Brand and G.A. van Es are employees of Cardialysis BV, The Netherlands. The other authors have no conflict of interest to declare.

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The references can be found on the online version of the paper.

Online data supplement

Supplementary appendix. Detailed description of SYNTAX and Leaman scores, and further case examples applying the CABG SXscore.

Online data supplement

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Scores

LEAMAN SCORE

The Leaman Score[64] is based on the severity of luminal diameter narrowing and is weighted according to the usual blood flow to the left ventricle in each vessel or vessel segment. In a right dominant system, the right coronary artery (RCA) supplies approximately 16% and the left coronary artery approximately 84% of the blood flow to the left ventricle. This 84% is normally directed 66% towards the left anterior descending (LAD) and 33% to the left circumflex (LCx) vessels. Consequently, the LMS, LAD and LCx supply approximately x5, x3.5 (84/16 x0.66) and x1.5 respectively as much blood as the RCA to the left ventricle, the values of which are designated as the respective vessel's segment-weighting factors. In a left dominant system, the RCA does not contribute to the blood supply of the left ventricle, which is instead supplied by the LCx. Thus the LMS supplies 100% of the blood flow to the left ventricle. Hence the LAD provides 58% (segment-weighting factor x3.5) and the LCx 42% (segment-weighting factor x2.5) of the total blood flow to the LV. These concepts ultimately formed the basis of the segment-weighting factors that were incorporated into the now validated SXscore[65-73].

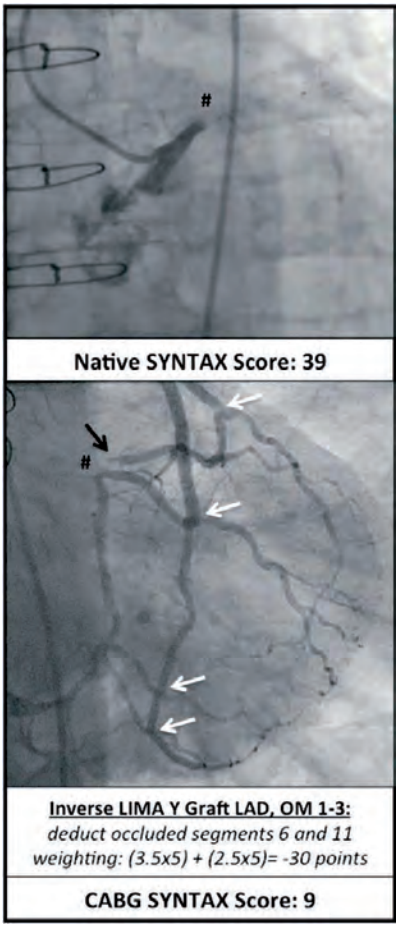
APPLICATION OF THE LEAMAN SCORE IN PATIENTS UNDERGOING CABG. Leaman et al previously applied the Leaman Score, derived from the segment-weighting factors, to patients at baseline and post CABG surgery[64]. This concept was based on the principle that the segment-weighting for the treated vessel would be deducted if it had a functioning bypass graft anastomosed distal to the treated lesion. For example, a significant mid RCA lesion would score a segment-weighting factor of 1x2 (2 points) if the lesion was significantly (non-total) diseased, or 1x5 (5 points) if the lesion was occluded. Post-surgery, if the graft to the RCA was patent, the respective segment-weighting points for the treated vessel would be deducted. Conversely, if the graft was occluded, the points would remain unaltered.

SYNTAX SCORE

The SXscore methodology has previously been described[74-77]. In brief, the SXscore was developed by combining the importance of a diseased coronary artery segment by the vessel-segment weighting (modified Leaman Score)[64], adverse characteristics of such a lesion for revascularisation (ACC/AHA lesion classification)[78,79] and the Medina classification system for bifurcation lesions[80,81].

Each vessel segment, 1.5 mm in diameter or greater, with a ≥50% diameter stenosis by visual estimation, is awarded a multiplication factor related to the location of the lesion, and the severity of the stenosis (non-total vs. total occlusion). Further characterisation of the coronary lesions leads to the addition of more points. These include features of total occlusions (duration, length, blunt stump, presence of bridging collaterals or side branch), the presence of bifurcation (based on the Medina classification) or trifurcation disease (number of diseased branches involved), side branch angulation, aorto-ostial lesion, severe tortuosity, lesion length >20 mm, heavy calcification, thrombus and diffuse or small vessel disease. The above information is entered into the online available SXscore algorithm[75] which automatically sums each of these features to calculate the total SXscore.

DEFINITIONS OF VESSEL SEGMENTS. A table of vessel segments relating to the SYNTAX Score is detailed hereafter **(Online Table 1)**.



Online Figure 1. *Example of the calculation of the CABG SXscore in a patient with an occluded LMS. Black arrows indicate obstructive native coronary disease; white arrows indicate patent anastomosis sites of grafts to vessels, # occluded LMS. LMS: left main stem; RCA: right coronary artery; LIMA: left internal mammary artery; OM: obtuse marginal; LAD: left anterior descending artery; SVG: saphenous vein graft*

Table 1. Definitions of segments.

1.	RCA proximal	From ostium to one half the distance to the acute margin of the heart.
2.	RCA mid	From end of first segment to acute margin of heart.
3.	RCA distal	From the acute margin of the heart to the origin of the posterior descending artery.
4.	Posterior descending artery	Running in the posterior interventricular groove.
16.	Posterolateral branch from RCA	Posterolateral branch originating from the distal coronary artery distal to the crux.
16a.	Posterolateral branch from RCA	First posterolateral branch from segment 16.
16b.	Posterolateral branch from RCA	Second posterolateral branch from segment 16.
16c.	Posterolateral branch from RCA	Third posterolateral branch from segment 16.
5.	Left main	From the ostium of the LCA through bifurcation into left anterior descending and left circumflex branches.
6.	LAD proximal	Proximal to and including first major septal branch.
7.	LAD mid	LAD immediately distal to origin of first septal branch and extending to to the point where LAD forms an angle (RAO view). If this angle is not identifiable this segment ends at one half the distance from the first septal to the apex of the heart.
8.	LAD apical	Terminal portion of LAD, beginning at the end of previous segment and extending to or beyond the apex.
9.	First diagonal	The first diagonal originating from segment 6 or 7.
9a.	First diagonal a	Additional first diagonal originating from segment 6 or 7, before segment 8.
10.	Second diagonal	Second diagonal originating from segment 8 or the transition between segment 7 and 8.
10a.	Second diagonal a	Additional second diagonal originating from segment 8.
11.	Proximal circumflex artery	Main stem of circumflex from its origin of left main to and including origin of (first and second) obtuse marginal branch(es).
12.	Intermediate/ anterolateral artery	Branch from trifurcating left main other than proximal LAD or LCx. Belongs to the circumflex territory.
12a.	Obtuse marginal a	First side branch of circumflex running in general to the area of obtuse margin of the heart.
12b.	Obtuse marginal b	Second additional branch of circumflex running in the same direction as 12.
13.	Distal circumflex artery	The stem of the circumflex distal to the origin of the most distal obtuse marginal branch and running along the posterior left atrioventricular grooves. Calibre may be small or artery absent.
14.	Left posterolateral	Running to the posterolateral surface of the left ventricle. May be absent or a division of obtuse marginal branch.
14a.	Left posterolateral a	Distal from 14 and running in the same direction.
14b.	Left posterolateral b	Distal from 14 and 14a and running in the same direction.
15.	Posterior descending	Most distal part of dominant left circumflex when present. Gives origin to septal branches. When this artery is present, segment 4 is usually absent.

Further illustrative examples of the application of the CABG SXscore

CASE 1

Occluded LMS (#) in a left dominant system gave a native SXscore of 39 (upper image). The ostial involvement of the LAD (black arrow) was regarded as part of the LMS lesion as it was located within ≥3 vessel reference diameters from the occluded LMS lesion. A patent LIMA inverse Y graft anastomosed to the mid LAD (upper white arrow), with sequential anastomoses to the 1st, 2nd and 3rd OM branches (lower three white arrows) are shown. Based on the segment-weighting 30 points were deducted from the native SXscore. Final CABG SXscore was therefore 39–17.5–12.5=9 points **(Online Figure 1)**.

CASE 2

Upper images: native SXscore was 35.5 with distal LMS disease (Medina 1.1.1), distal RCA disease, and an occluded ostial LCx (#). Lower images: distal RCA protected by SVG (left image), therefore 1x2 points were deducted from the native SXscore. Occluded ostial LCx is under "ischaemic protection" by the RIMA to the distal OM (middle image) secondary to disease more proximal to the anastomosis. Therefore 1.5x3 points are deducted from the native SXscore (no points are added for the OM disease as it is protected by the RIMA graft). The ostial LAD disease is protected by the LIMA (right image) anastomosed to the distal LAD with no intervening obstructive disease, so 3.5x2 points are deducted from the native SXscore. Final CABG SXscore was therefore 35.5–2–4.5–7=22 points **(Online Figure 2)**.

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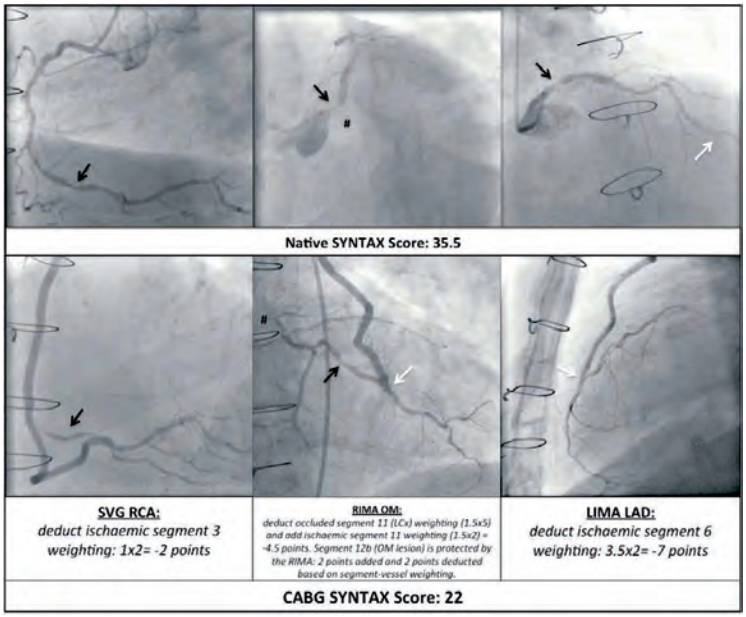

Online Figure 2. *Example of the calculation of the CABG SXscore in a complex case. Black arrows indicate obstructive native coronary disease; white arrows indicate patent anastomosis sites of grafts to vessels. LMS: left main stem; RCA: right coronary artery; LIMA: left internal mammary artery; RIMA: right internal mammary artery; LCx: left circumflex; OM: obtuse marginal; LAD: left anterior descending artery; SVG: saphenous vein graft*

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6.4

The coronary artery bypass graft SYNTAX Score: final five-year outcomes from the SYNTAX-LE MANS left main angiographic substudy.

Farooq V, Girasis C, Magro M, Onuma Y, Morel MA, Heo JH, Garcia-Garcia HM, Kappetein AP, van den Brand M, Holmes DR, Mack M, Feldman T, Colombo A, Ståhle E, James S, Carrié D, Fournial G, van Es GA, Dawkins KD, Mohr FW, Morice MC, Serruys PW.

EuroIntervention. 2013 Dec;9(8):1009-10

The coronary artery bypass graft SYNTAX Score: final five-year outcomes from the SYNTAX-LE MANS left main angiographic substudy

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We recently reported the coronary artery bypass graft (CABG) SYNTAX Score, an objective measure of anatomical complexity and revascularisation post coronary artery bypass graft (CABG) surgery[1]. At four-year follow-up, a non-significant trend towards more adverse clinical outcomes, including all-cause death, was reported in the higher CABG SYNTAX group (≥22)[1]. The final five-year outcomes of the SYNTAX trial have recently been reported[2,3]. We report the five-year outcomes of the CABG SYNTAX Score from the CABG arm of the SYNTAX-LE MANS left main angiographic substudy.

At five years, significantly greater all-cause death was seen in the high CABG SYNTAX Score group (≥22) compared to the low CABG SYNTAX Score group (<22) (14.5% vs. 9.1%, log rank p-value=0.012) **(Figure 1)**. Similarly, significantly greater five-year all-cause death/cerebrovascular accident (CVA)/myocardial infarction (MI) (log rank p-value=0.025) and MACCE (major adverse cardiac and cerebrovascular events) (log rank p-value=0.050) were reported.

Incomplete revascularisation (ICR) has recently been hypothesised and shown to be a surrogate marker of a greater burden and complexity of coronary disease, other vascular disease, and clinical comorbidity, in both CABG and PCI (percutaneous coronary intervention) treated patients[4,5]. Specifically, in the all-comers CABG and PCI arms of the SYNTAX trial, adverse long-term (four-year) clinical outcomes – including mortality, all-cause revascularisation, and MACCE – were shown to occur more frequently in patients who were incompletely revascularised.

The CABG SYNTAX Score and its PCI equivalent, the residual SYNTAX Score[6], both provide objective measures of the complexity of the residual disease and level of revascularisation. These scores may aid in determining a level of "reasonable revascularisation" after undergoing surgical or percutaneous-based revascularisation[7], and may have a long-term prognostic role in identifying high-risk patients undergoing CABG or PCI. Validation studies are awaited.

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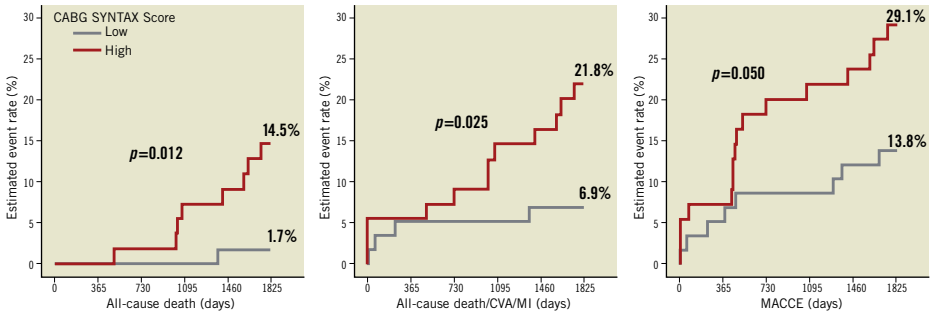

Figure 1. *Outcomes (Kaplan-Meier curves) separated by the median of the CABG SYNTAX Score into low (0-21) (n=58) and high (≥22) (n=55) score groups. At 5 years, significantly greater all-cause mortality (left image), significantly greater all-cause death/CVA/MI (middle image) and MACCE (right image) were evident in the high CABG SYNTAX Score group compared to the low CABG SYNTAX Score group. Note the peak in MACCE at approximately 18 months secondary to patients undergoing scheduled coronary angiography, the findings of which triggered repeat revascularisation. Log rank p-values are shown.*

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Conflict of interest statement

K. Dawkins is a full-time employee of, and holds stock in, Boston Scientific. M. Mack has served on the speakers bureau of Boston Scientific, Cordis and Medtronic. T. Feldman has served on the speakers bureau of Boston Scientific; has received grant support from Abbott, Atritech, Boston Scientific Corporation, Edwards, and Evalve; and has worked as a consultant for Abbott, Coherex, Intervalve, Square One, and WL Gore. M-A. Morel's institution has received a research grant from Boston Scientific. M-A. Morel, H.M. Garcia-Garcia and G.A. van Es are employees of Cardialysis. The other authors have no conflicts of interest to declare.

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Part VII

PERCUTANEOUS CORONARY INTERVENTION IN BIFURCATIONS INCLUDING THE LEFT MAIN STEM

7.1

The Tryton side branch stent.

Magro M, van Geuns RJ.

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The Tryton Side Branch Stent

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The authors have no conflicts of interest to declare.

Abstract

The Tryton Side Branch Stent (Tryton Medical, Durham, NC, USA) is a dedicated bare metal stent developed to enhance the safety and efficacy of the two stent technique for the treatment of bifurcation lesions. The stenting technique, a "reverse culotte", secures the side branch (SB) with the placement of this dedicated stent in the proximal main vessel, across to the side branch while it facilitates the positioning of a conventional stent in the proximal to distal main vessel. The First-In-Man trial showed minimal SB late loss (0.17±0.35 mm) at six months while real world registry data reported target vessel revascularisation rates as low as 4% at the same time points and no stent thrombosis. The simplicity of the technique as well as the promising results have led to its widespread utilisation in Europe while in the US, a randomised trial is imminent and will serve for the device approval by the Food and Drug Administration.

The device

The stent is composed of the alloy cobalt chromium which allows 0.003 inch or 76.2 µm thin struts. The modular design has three distinct zones; a distal side branch zone, a central transition zone and a proximal main vessel zone. The distal zone has a standard slotted tube workhorse stent design; the central transition zone consists of three panels while the proximal main vessel zone is composed of three undulating fronds that terminate proximally in a circumferential "wedding" band. In a recent version a second wedding bend has been added as illustrated in Figure 1. Currently only one stent length of 19 mm is available. The stent is balloon expandable and is mounted either on a semi-compliant balloon with uniform diameter of 2.5 mm or on a stepped balloon with a diameter of 3.0 or 3.5 mm proximally and 2.5 mm distally. The stent delivery system has four markers to delineate the proximal and distal end of the stent as well as the proximal and distal extent of the transition zone.

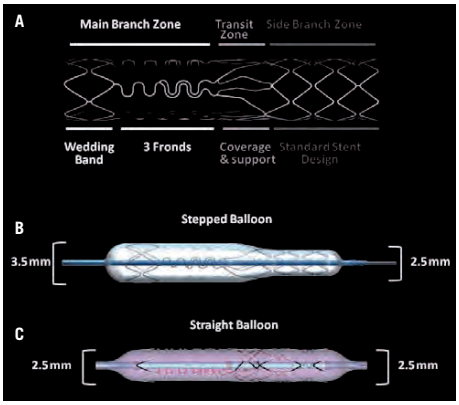

Figure 1. The Tryton Side Branch Stent. A. The stent has three distinct regions with specific design characteristics. The newer generation has two proximal wedding bands. B. Stepped balloon allows stent deployment in side branches with significantly smaller diameters than the proximal main vessel. C. Straight balloon for deployment in similar sized main and side branches.

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Stenting technique

The procedure is usually performed via a 6 Fr guiding catheter although the system is also compatible with a 5 Fr. A sequence and corresponding example are illustrated in Figure 2. After wiring of both main vessel and side branch and predilatation, the Tryton Side Branch Stent is advanced over the wire into the side branch, and using the two middle markers on the delivery system, the stent is positioned till these markers straddle the side branch origin. Deployment of the stent is followed by retraction of the guidewire from the side branch and repositioning it through the fronds of the transition zone into the distal main vessel. A standard stent is then advanced and positioned in the main vessel jailing the stented side branch. Once the main vessel stent is deployed re-crossing into the side branch allows final kissing balloon inflation.

Clinical data

Tryton I – First-In-Man trial

The FIM trial enrolled 30 patients with stable coronary artery bifurcation disease at three European centres.[1] Six months clinical follow-up was available in 100% with angiographic follow-up performed in 78%. The primary endpoint that was defined as freedom from major adverse cardiac events (MACE) following procedural success was met in 93.3%. The MACE rate at six months was 9.9%. Quantitative coronary angiography (QCA) with a dedicated bifurcation software analysis (CAAS 5.5; Pie Medical Imaging, Maastricht, The Netherlands) demonstrated late luminal loss of 0.17±0.35 mm with no re-stenosis in the side branch. Late Loss in the proximal main branch was 0.24±0.43 mm while that in the distal main branch was 0.00±0.31 mm. This study clearly showed that the technique is feasible and the device is safe and effective when combined with a standard drug-eluting stent. (Cypher; Cordis, Johnson & Johnson, Warren, NJ, USA and Taxus; Boston Scientific, Natick, MA, USA – in this study). No cases of stent thrombosis occurred during follow-up.

Rotterdam – Poznan registry

A two centre registry (Rotterdam, Netherlands and Poznan, Poland) including 100 bifurcation lesions in 96 consecutive patients has evaluated the safety and efficacy of the stent system in the real world.[2] In contrast with the FIM study, patients with acute coronary syndrome including ST elevation myocardial infarction, chronic total

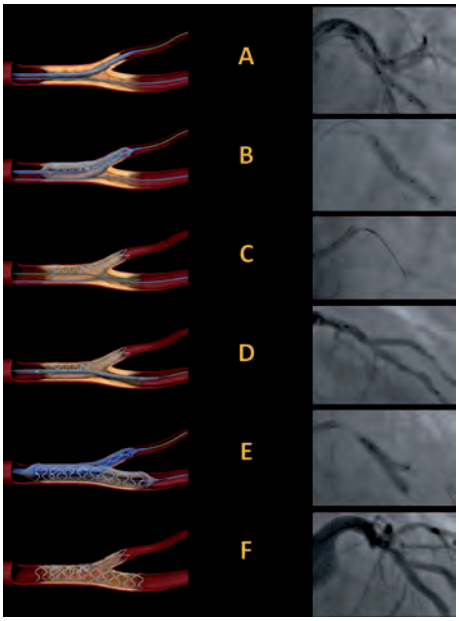

Figure 2. Schematic illustration of the reverse culotte stenting technique with the Tryton Side Branch Stent and a corresponding angiographic appearance from a patient treated for a left anterior descending /diagonal bifurcation lesion. A. Positioning of the Tryton stent is optimised by placing the middle markers equidistant from the carina; B. Inflation of the stepped balloon deploys the stent; C. Retraction of the side branch wire and re-cross into the distal main vessel; D. positioning of the main vessel stent is followed by deployment of the stent; E. Wire re-cross into the side branch allows final kissing balloon inflation; F. Final result.

occlusions, saphenous grafts and interestingly left main bifurcation lesions were included. Also the standard workhorse stent type used for the main branches differed significantly. The rate of final kissing balloon was also lower at 71%. Acute gain in SB was 0.76±0.64 mm and three patients had residual stenosis of >30%. Angiographic success rate was 95%; procedural success rate reached 94%. Periprocedural MI occurred in two and there was one cardiac death during hospitalisation. At a median six months follow-up, TLR rate was 4%, MI 3% and cardiac death 1%. The percentage MACE-free survival at six months was 94%. Again no cases of definite stent thrombosis occurred confirming the safety of this bifurcation treatment strategy. A case example assessed by optical coherence tomography is shown in Figure 3.

E-Tryton

The interim results from the E-Tryton registry, a European multicentre registry with 15 active centres were recently presented at the Transcatheter Cardiovascular Therapeutics conference in Washington, USA.[3] In 301 implantations, the rate of periprocedural myocardial infarction was 1.4% and procedural success defined as successful implantation of the Tryton stent and main branch stent without in-hospital MACE was 98.3%. Six month follow-up was available in patients treated with the Tryton Side Branch Stent. Of the 253 patients who reached six month follow-up, two (0.8%) sustained a non-Q-wave myocardial infarction while nine (3.6%) required target lesion revascularisation. Of these six (2.4%) occurred in the main branch while three (1.2%) occurred in the side branch. As in the Rotterdam-Poznan registry, no cases of stent thrombosis were reported.

IUVANT Study

The Tryton II – IUVANT (Intravascular Ultrasound Evaluation of the Tryton stent) study enrolled 32 consecutive patients with 33 bifurcation lesions treated with the Tryton Side Branch Stent in conjunction with Xience V or PRIME everolimus eluting stent (Abbott Vascular, Santa Clara, CA, USA).4 Kissing balloon inflations were accomplished in all patients while post-procedural intravascular ultrasound (IVUS) was performed at baseline and at nine months follow-up. The results of the first 27 patients were presented at TCT 2010. IVUS defined stent expansion (minimum stent area/average lumen area) was high in both main vessel (MV) and side branches (SB) and showed complete scaffolding of SB ostium. Neo-intimal hyperplasia at nine months measured respectively 0.33±0.0 mm^2 and 0.73±0.54 mm^2 in the MV and SB.

Personal perspective

In treatment of bifurcation lesions, the major concern among the most of experienced interventional cardiologists is preservation of side branch patency. The Tryton Side Branch Stent and its strategy tackles this from the outset and while it secures the sidebranch[5]; it

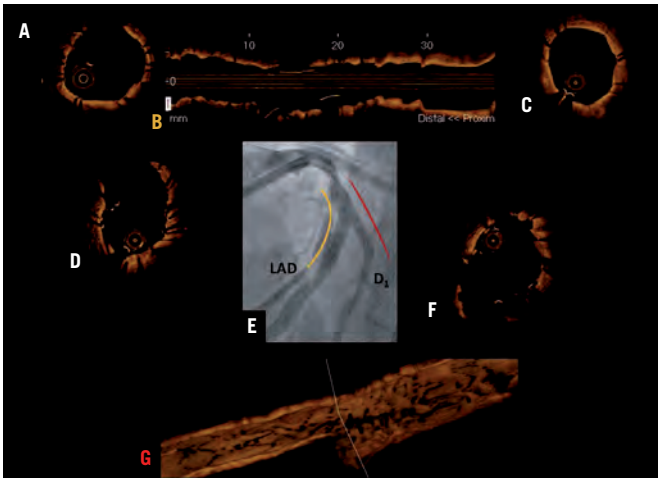

Figure 3. Optical coherence tomography evaluation of a left anterior descending/diagonal bifurcation stenting with the Tryton Side Branch Stent in conjunction with a XIENCE V stent. A. Good apposition of the Xience V struts in the distal left anterior descending artery (LAD); B. longitudinal view of the pullback through the main vessel. Note the side branch wire marked with a black arrow. C. Stent struts a the proximal main vessel where minimal overlap occurs between struts of the two stents ensuring good apposition; D and F show the frame with maximal lumen area view at the ostium of the bifurcation from the LAD pullback and the diagonal pullback respectively. Note minimal presence of luminal struts in these images; E. Final angiographic appearance; F. Three dimensional rendering from OCT pullback starting in the diagonal branch. The Tryton stent design, particularly the distal region and transition zone can be appreciated in this view. In the proximal main vessel the proximal part of the Tryton stent is seen to be covered by the XIENCE V stent struts.

facilitates main vessel stenting through the purposely designed fronds at the carina area. Once the side branch is successfully wired, the stent has excellent deliverability, easy guiding for accurate positioning with radio-opaque markers and a generous landing zone (4 mm) which all contribute to successful side branch stenting. There is no need for rotational orientation, and single-wire-tracking means that wire wrapping is not an issue when compared to some of the other dedicated bifurcation stents. Wiring of the main vessel is rendered easy by the presence of only three fronds in the proximal part of the Tryton stent. Kissing balloon inflation is recommended to ensure optimal stent apposition at the actual bifurcation and minimise residual luminal stent struts. This requires re-crossing through a conventional stent into the side branch which may be tedious; however tips and tricks such as guidewire curvature re-shaping and post-dilation of the proximal main vessel with a short balloon that widens the struts jailing the SB, may facilitate wire crossing that allows subsequent final kissing. The wide range of bifurcation angles that the stent system can be used in makes this stenting strategy applicable to a wide range of bifurcation locations and MEDINA bifurcation types. It is particularly attractive for true bifurcation lesions as well as for left main stenting in which early and mid-term outcome from our experience is very positive. In fact the company is in the process of manufacturing different sized stents (both wider – 3.5 and 4.0 mm – and shorter) that better suit the left main stem coronary anatomy.

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7.2

Six-month clinical follow-up of the Tryton side branch stent for the treatment of bifurcation lesions: a two center registry analysis.

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Six-Month Clinical Follow-Up of the Tryton Side Branch Stent for the Treatment of Bifurcation Lesions: A Two Center Registry Analysis

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Background: Treatment of bifurcation lesions with the Tryton Sidebranch stent has been shown to be feasible with an acceptable clinical outcome and low side branch late loss in the first in man trial. **Objective:** To report acute procedural and six month clinical follow-up after the use of the Tryton Sidebranch stent in an "all comer" registry. **Methods:** The first 100 coronary bifurcation lesions assigned for treatment with the Tryton stent were included in a prospective registry. Procedural and angiographic success rates were determined from patient charts and pre- and postprocedural quantitative coronary angiography. **Results:** Totally, 96 patients with 100 lesions were included in the study. Seventy-two percent presented with stable angina, 25% with unstable angina/NSTEMI, and 3% STEMI. The bifurcation was located in the left main in 8%. Two lesions were chronic total occlusions. Sixty-nine percent were true bifurcation lesions. One failure of stent delivery occurred. Acute gain in SB was 0.76 ± 0.64mm and three patients had residual stenosis of >30%. Angiographic success rate was 95%; procedural success rate reached 94%. Peri-procedural MI occurred in two and there was one cardiac death during hospitalization. At a median six months follow-up, TLR rate was 4%, MI 3%, and cardiac death 1%. The percentage MACE-free survival at six months was 94%. No cases of definite stent thrombosis occurred. **Conclusions:** In a real world the use of the Tryton Sidebranch stent is associated with good procedural safety and angiographic success rate and acceptable outcome at six months of follow-up.

Key words: bifurcation lesions; percutaneous coronary intervention; procedural success; six month MACE

INTRODUCTION

Percutaneous coronary intervention (PCI) for bifurcation lesions is considered high risk with increased procedural adverse events as well as inferior long term outcome when compared to non-bifurcation intervention [1]. Several techniques and strategies have been explored, employing one or two conventional tubular stents but the improvement in outcome remains limited. This is primarily reflected in the increased rates of sidebranch restenosis [2]. Dedicated bifurcation stents, specifically designed to allow minimally traumatic implantation in the main vessel and/or sidebranch while providing adequate scaffolding of the

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Conflict of interest: Nothing to report.

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sidebranch ostium may offer an advantage over utilisation of conventional stents [3].

The Tryton Side-Branch Stent (Tryton Medical, Inc., Newton, MA) is a dedicated bifurcation stent inspired by the "culotte" stenting technique [4]. This Tryton Side-Branch stenting strategy showed acceptable clinical outcome with no sidebranch restenosis and low side-branch late loss (0.17 ± 0.35 mm) at six months in the First-in-Man (FIM) trial that enrolled 30 patients with stable coronary artery disease and de novo bifurcation lesions. Being a FIM, the study had restricted inclusion criteria that does not represent routine clinical practice [5].

The present registry analysis was conducted to evaluate the procedural success and to assess clinical outcome of bifurcation stenting with the Tryton Side-Branch Stent™ in conjunction with a standard workhorse stent in a "real world," all comer population.

METHODS

Patient Population

All patients with ischaemia in a myocardial segment supplied by a coronary artery with a bifurcation lesion with disease in both main vessel and sidebranch that were referred for PCI from December 2006 at two academic tertiary hospitals in the Netherlands (Thoraxcenter, Erasmuc MC, Rotterdam) and Poland (University Hospital of Lord's Transfiguration, Poznan) were eligible. Specifically the bifurcation could be located anywhere in the coronary circulation including grafts. The visually estimated reference diameter of the main vessel could be 2.5–5.0mm and that of the sidebranch in the range 2.0–2.75 mm. These dimensions were selected to comply with the available sizes of the Tryton stent. However the decision to treat the bifurcation and employ a Tryton Side Branch Stent remained at the discretion of the treating interventional cardiologist. The first 100 lesions assigned for treatment with the Tryton Sidebranch Stent were included in a collaborative registry between the two institutions.

Study Device and PCI strategy

The Tryton Side-Branch Stent is a slotted tube, balloon expandable cobalt chromium BMS with three zones: a distal sidebranch zone, a central transition zone and a proximal main vessel zone. The distal zone has a standard slotted tube workhorse stent design, the central transition zone consists of three panels while the proximal main vessel zone is composed of three fronds that terminate proximally in a circumferential band. The stent is mounted either on a balloon with a uniform diameter of 2.5 mm (straight type) or on a stepped balloon with a diameter of 3.5 mm proximally and 2.5 mm distally (tapered type). The stent delivery system has four markers to delineate the proximal and distal end of the stent as well as the proximal and distal part of the transition zone. Further details of the stent design as well as the standard technique for implantation have been published [4]. In short, the procedure is typically performed via a 6Fr guiding catheter; after optional wiring of both main vessel and sidebranch for predilation, the Tryton stent is advanced over the wire into the sidebranch, and using the two middle markers on the delivery system, the stent is positioned till these markers straddle the carina. Deployment of the stent is followed by retraction of the guidewire from the sidebranch and repositioning it through the fronds of the transition zone into the distal main vessel. A standard stent is then advanced and positioned in the main vessel jailing, the stented sidebranch. Once the main vessel stent is deployed, recrossing into the sidebranch allows final kissing balloon inflation.

Procedure

Patients were pretreated with aspirin (75 mg) and clopidogrel (300–600 mg) unless they were already taking these antiplatelet agents. Intravenous heparin was administered to maintain an activated clotting time of >250 sec. Glyoprotein IIb/IIIa inhibitor use was left to the treating interventional cardiologist's discretion as was the use of other additional devices such as thrombectomy, excimer laser, rotablator etc. Delivery failures, need for additional overlapping stents to cover the whole lesion, additional ballooning, and procedural angiographic and clinical complications were noted. Aspirin was continued indefinitely and clopidogrel was continued for 12 months after the index procedure.

Cardiac Enzymes and ECG

Serial cardiac enzymes including creatinine kinase (CK)-MB mass, troponin-T, or troponin-I were measured after the procedure. Preprocedure biomarkers were assessed in all patients with acute coronary syndrome. These patients were included in the biomarker analysis only if preprocedure markers were normal. A 12 lead ECG was obtained before and after procedure as part of routine institutional practices.

Quantitative Coronary Angiography

Angiographic films were analysed with a dedicated bifurcation software (CAAS 5.5, Maastricht, PIE Medical software, The Netherlands) [6]. Reference vessel diameter, minimal luminal diameter (MLD) and percentage diameter stenosis were obtained for the

proximal main vessel (PMV), distal main vessel (DMV), and sidebranch (SB) in the preprocedural angiographic film. Matched views of immediate post-procedural films were then selected for determination of the same parameters. Acute gain was determined from the difference between MLD in each of the three segments (PMV, DMV, SB).

Follow-Up

Survival data from all patients were obtained from municipal civil registries. A health questionnaire was subsequently sent to all living patients with specific questions on treatment compliance, readmission and major adverse cardiac events. Patients who did not send the filled questionnaire were contacted by phone to obtain the relevant information. Those who reported events had their medical records, discharge summaries and any repeat angiographic films systematically reviewed. Data was carefully verified and adjudicated by cardiologists according to criteria defined below.

Definitions

Primary device success was defined as successful deployment of the intended stent without system failure or device related complication. Angiographic success was defined as <30% residual stenosis and TIMI 3 flow in both main vessel and sidebranch after the procedure. Procedure success included angiographic success in the absence of in-hospital major adverse cardiac events (MACE). MACE was defined as a composite of cardiac or noncardiac death, Q-wave, or non-Q-wave myocardial infarction (MI) and ischaemia driven target lesion revascularisation (TLR). Non-Q wave MI was defined as clinical signs of myocardial infarction associated with a CK-MB mass or troponin -T/troponin-I increase to more than three times the upper limit of normal in the absence of Q waves and not related to an interventional procedure. Q-wave MI occurred when there was chest pain or symptoms consistent with myocardial ischaemia and new pathological Q waves in two or more contiguous electrocardiograph leads. TLR was defined as any PCI of the index lesion and including the 5 mm persistent segments in either main vessel or sidebranch. Target vessel revascularisation (TVR) was defined as revascularization of any part of the index coronary artery. Stent thrombosis was defined according to the Academic Research Consortium (ARC) [7].

Statistical Analysis

Continuous data are expressed as mean ± SD or as median (interquartile ranges) whereas dichotomous data are summarized as frequencies. The Kalpan-Meier method was used to study the incidence of events over time relative to the number of patients at risk at each time point. Statistical analysis was performed using SPSS software version 17.0 (SPSS, Chicago, USA)

TABLE I. Baseline Clinical Characteristics

Characteristics	$N = 96$
Male	72 (75%)
Age, years (mean ± SD)	63.9 ± 8.8
Diabetes mellitus	30 (31%)
Hypertension	58 (60%)
Hypercholesterolaemia	60 (63%)
Family history of coronary artery disease	46 (48%)
Smoker	17 (18%)
Previous myocardial infarction	42 (44%)
Previous PCI	40 (42%)
Previous CABG	8 (8%)
Stable angina	69 (72%)
Unstable angina	24 (25%)
ST elevation myocardial infarction	3 (3%)

Data are presented as numbers (percentages) or mean ± SD unless specified. Percentages have been rounded.

RESULTS

One hundred bifurcation lesions in 96 patients were included between December 2006 and March 2010. Baseline characteristics of patients included are shown in Table I. The mean age of patients was 63.9 years and the majority were male (75%). While most patients presented for PCI with stable angina (72%), three patients were treated for an acute myocardial infarction.

Lesion characteristics are described in Table II. Sixty-six percent of patients had multivessel disease and five patients had two bifurcation lesions that needed revascularization. Most bifurcations targeted for treatment with the Tryton Sidebranch stent were located in the left anterior descending/diagonal junction (72%). Eight stents were implanted in the left main coronary arteries. Two bifurcations involved the anastomosis of a saphenous venous graft with a native coronary artery; in one on the posterior descending and the other on the left anterior descending artery. A left anterior descending/large septal branch bifurcation was also included. Two bifurcations were treated after successful crossing of a chronic total occlusion in two patients. Sixty-nine percent of lesions were true bifurcation lesions (1,0,1 or 1,1,1 or 0,1,1) with involvement of both the main vessel and the sidebranch.

The mean reference diameters for the proximal main branch (PMB), distal main branch (DMB) and side branch (SB) were 2.91, 2.46, and 2.22 mm, respectively. The mean percentage diameter stenosis obtained

TABLE II. Lesion Characteristics

Lesions	$N = 100$
Bifurcation location	
Left main	8
Left anterior descending/diagonal	72
Left circumflex/obtuse marginal	11
Posterolateral/posterior descending	5
Saphenous vein graft/native vessel	2
Other	2
Medina classification	
1,0,0	10
1,1,0	11
0,1,0	3
0,0,1	6
1,0,1	13
0,1,1	3
1,1,1	54
ACC classification	
A	0
B1	28
B2	39
C	33
Multivessel disease[a]	62 (66%)
Chronic total occlusion	2

Data represents actual number which is equivalent to the percentage since the number of lesions is 100 unless specified.
[a]62 patients out of 96 had disease in a vessel other than the one with the index bifurcation.

TABLE III. Quantitative Angiographic Parameters Pre and Postprocedural ($n = 100$)

Parameter	Preprocedure	Postprocedure
Proximal main branch		
MLD (mm)	1.49 ± 0.76	3.09 ± 0.48
Reference diameter (mm)	2.91 ± 0.62	3.32 ± 0.56
% Diameter stenosis	49 ± 24	8 ± 8
Acute gain (mm)		1.62 ± 0.74
Distal main branch		
MLD (mm)	1.43 ± 0.74	2.54 ± 0.44
Reference diameter (mm)	2.46 ± 0.52	2.77 ± 0.44
% Diameter stenosis	41 ± 29	8 ± 8
Acute gain (mm)		1.12 ± 0.77
Sidebranch		
MLD (mm)	1.30 ± 0.56	2.04 ± 0.36
Reference diameter (mm)	2.22 ± 0.40	2.31 ± 0.35
% Diameter stenosis	40 ± 26	12 ± 11
Acute gain (mm)		0.76 ± 0.64
Bifurcation angles in degrees		
PMB and SB	151.6 ± 1.5	
DMB and SB	52.5 ± 0.5	

Data is expressed in mean ± SD. MLD, minimal luminal diameter; PMB, proximal main branch; DMB, distal main branch; SB, sidebranch.

by including all bifurcations, irrespective of the presence of significant disease in the three segments, were 49%, 41%, and 40% for PMB, DMB, and SB, respectively. The mean angle between the PMB and the SB was 152° while that between the DMB and the SB was 53°. These pre-procedural quantitative coronary angiographic measurements are presented in Table III.

Ninety-nine of the 100 Tryton Sidebranch stents intended for treatment of 100 bifurcation lesions were successfully implanted resulting in a 99% device success rate. A case example is illustrated in Fig. 1 with corresponding optical coherence tomography images (Lightlab Imaging, Westford, MA) in Fig. 2. The tapered balloon delivery system was used in 93% of the procedures. Table IV lists the various types of stents used as the workhorse principal main vessel stent. Two patients received a bare metal stent. Procedural characteristics are shown in Table V. The mean nominal diameter of the main vessel stent was 3.0 ± 0.5 mm with a mean length of 24 ± 6 mm. Additional stents overlapping the Tryton stent in the sidebranch were deployed in 16% while in 19% of lesions further overlapping stents were implanted in the main vessel. Predilation was performed in 90% while final "kissing" ballooning was done in 71%.

Angiographic success was achieved in 95%; one failure of Tryton stent delivery with subsequent dissection in a diagonal sidebranch while four lesions did not meet the predefined angiographic success criterion of 30% residual stenosis. In these four lesions 38–47% residual stenosis on QCA was measured, mainly caused by a disproportionate increase in the distal sidebranch vessel diameter by insertion of an additional stent. Periprocedural PCI-related MI occurred in the same patient who had unsuccessful delivery of the stent. Another patient who presented with acute myocardial infarction with cardiogenic shock and who had a bifurcation treated with good angiographic result died within 48 hours of the procedure. Therefore the procedure success was 94%.

The QCA parameters for the whole cohort pre and post procedure are listed in Table III. The mean acute gain in the sidebranch was 0.76 ± 0.64 mm. On analysis of a subgroup of bifurcations ($n = 76$) with true sidebranch disease (1,0,1; 1,1,1; 0,1,1 and 0,0,1), the mean acute gain was 0.94 ± 0.60 mm.

In-Hospital and Mid-term Clinical Outcome

The clinical events are summarized in Table V. In-hospital MACE rate reached 3%. The only case of death was due to cardiac death in the patient treated for STEMI with cardiogenic shock as mentioned above. Postprocedural elevations of troponins occurred in 11/33 patients treated for stable angina but two met criteria of a PCI related myocardial infarction. The first occurred secondary to dissection of the diagonal branch in which the Tryton stent could not be delivered. The second occurred secondary to transient slow flow in the distal main branch after placement of the main

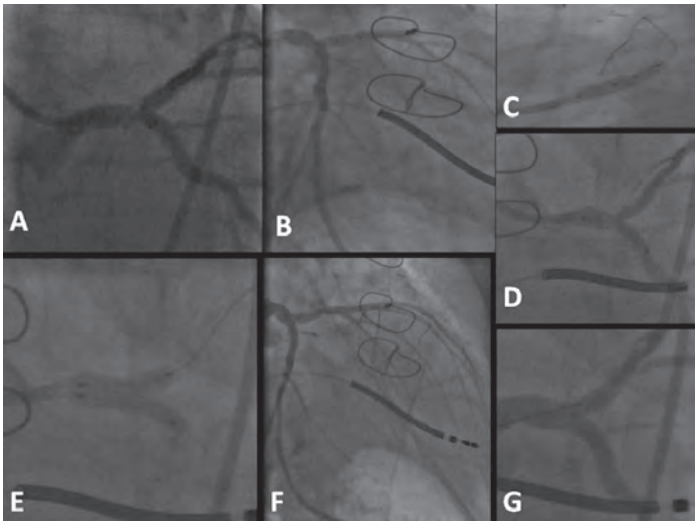

Fig. 1. Case example of a Tryton Side Branch Stent insertion in the left main (LM) coronary bifurcation. A: Diagnostic angiogram of a patient with previous left internal mammary graft to the left anterior descending artery, and persistent ischaemia, showing significant disease at the LM bifurcation. B: Positioning of the Tryton stent in the smaller calibre left anterior descending artery, in this case considered the Side Branch. Note the straddling of the carina with the middle two markers. C: Deployment of Tryton by inflation of the stepped balloon. Guide wire retraction and redirection into the dominant larger left circumflex artery (main vessel) was followed by deployment of a standard drug eluting stent with proximal part in LM and distal part in left circumflex (D). Wire recross into side branch and fenestration with small balloon allowed final kissing balloon inflation (E). Angiographic result at the end of procedure (F, G).

vessel stent. There were no cases of definite/probable stent thrombosis or target vessel revascularization.

Thirty-day follow-up was available in all patients. There were no reported events and therefore the MACE is same as the in-hospital outcome.

Patients were followed up for a median of six months. All patients were compliant with their prescribed medications at the time of last contact. Fifty-one patients had at least six months follow-up. Up to this time point, one patient suffered a myocardial infarction due to occlusion of a vessel other than that treated in the index procedure 78 days earlier. The same patient had TLR of SB at 155 days. A second patient had a TLR so that the percentage of survival free of MACE at six months was 94% as shown in the Fig. 3. Two other patients with longer than six months follow-up had ischaemia-driven target lesion revascularization (194 and 292 days). Restenosis occurred in the main vessel in two patients and in the side branch in the other two. No cases of stent thrombosis were reported. Thus the cumulative MACE rate over a median follow-up period of 206 days (IQR: 125-386) at follow up reached 8% as shown in Table V.

DISCUSSION

This registry comprising an "all comer" population with implantations including three for acute myocardial infarctions, eight left main lesions, and two chronic total occlusions, has shown that the Tryton side branch stent, used in conjunction with a standard workhorse stent for the treatment of complex bifurcation lesions has resulted in a good procedural success rate (94%) and acceptable 8% MACE rate at six months follow-up. More specifically PCI related MI was limited to 2%, the TLR rate at follow up was just 4% and importantly, there were no cases of stent thrombosis.

Bifurcation intervention is historically associated with worse outcome [1,8]. Although stenting has improved the prognosis and DES have further improved it, restenosis and pinching of the side-branch often triggers the need to intervene on the sidebranch. In a bifurcation registry study by Kaplan et al., 80 of 288 (27.8%) bifurcation lesions treated with one stent initially required a second stent due to severe impairment of the SB during the angioplasty procedure [9]. Despite technical improvements in the use of two stent techniques, recent randomized

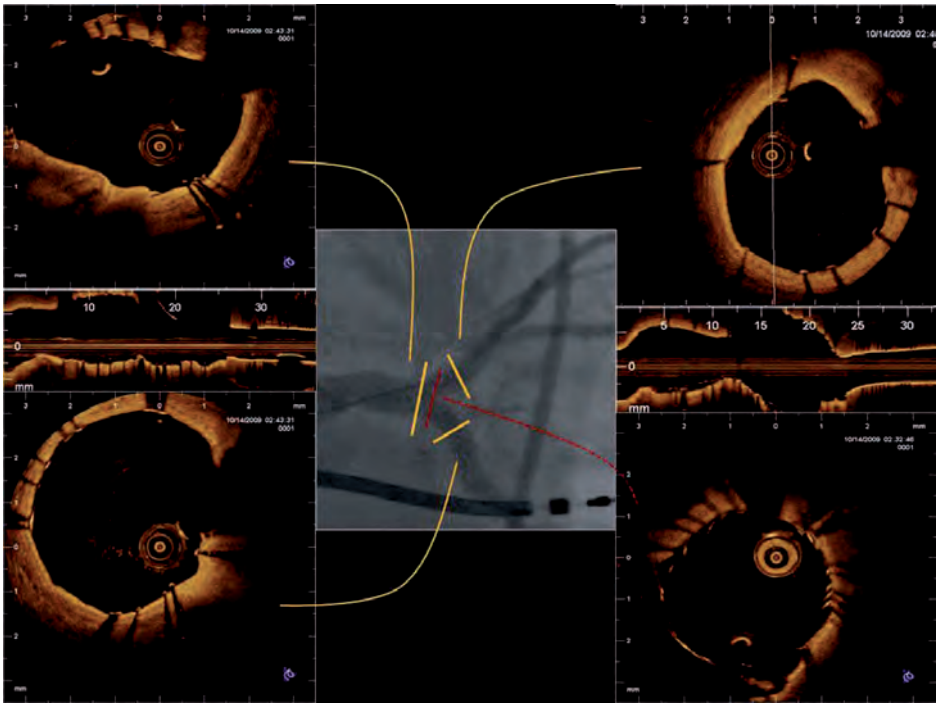

Fig. 2. Optical coherence tomography performed after treatment of the left main coronary artery bifurcation described in Fig. 1. Pullback from the left anterior descending artery shows good apposition of the Tryton stent (right upper panel). Pullback from the left circumflex artery also shows good standard stent apposition in left circumflex (right lower panel). Left main coronary imaging shows minimal strut overlap (left upper panel). Imaging at the bifurcation also reveals satisfactory strut apposition (right lower panel).

TABLE IV. Main Vessel Stents Implanted

Stent name	Manufacturer	Drug eluted	Frequency
Xience V	Abbott Vascular, Santa Clara, CA	Everolimus	47
Xience Prime	Abbott Vascular, Santa Clara, CA	Everolimus	17
Taxus Liberté	Boston Scientific, Natick, MA	Paclitaxel	13
ENDEAVOR resolute	Medtronic Vascular, Santa Rosa, CA	Zotarolimus	7
Cypher Select	Cordis Corp, Warren, NJ	Sirolimus	6
Promus	Boston Scientific, Natick, MA	Everolimus	3
Biomatrix	Biosensors International, Singapore	Biolimus A9	1
Coroflex Please	B. Braun, Melsungen, Germany	Paclitaxel	1
Luc - Chopin	Balton, Warsaw, Poland	Paclitaxel	1
Skylor	Invatec, Brescia, Italy	None	1
Vision	Abbott Vascular, Santa Clara, CA	None	1

trials failed to show any advantage over the use of one stent technique in terms of clinical outcome. More so, the provisional one stent technique is associated with lower procedural cardiac biomarker release, lower contrast dose used, and less radiation used [10–12].

TABLE V. Procedural and Clinical Outcome

Predilation	
Side branch	69 (70%)
Main vessel	83 (84%)
Separate postdilation	71 (72%)
Final kissing	70 (71%)
Additional overlapping stent implantation[a]	
Side branch	15 (16%)
Main vessel	19 (20%)
Total stents implanted	275
Stents per bifurcation	2.4 ± 0.7
Stents per patient	2.9 ± 1.3
Multivessel stenting in index procedure	26 (26%)
Acute procedural outcome	$N = 100$
Device success	99
Angiographic success	95
PCI related biomarker elevation	11/33 (33%)
PCI related MI	2
Procedural success	94
In-hospital outcome[b]	$N = 96$
Cardiac death	1
Myocardial infarction	2
CABG	0
Target lesion revascularization	0
Target vessel revascularization	0
Definite/probable stent thrombosis	0
Cardiac death or MI	2
MACE (cardiac death, MI, CABG or TLR)	2
Median six month outcome (cumulative)[b]	$N = 96$
Cardiac death	1
Myocardial infarction	3
CABG	0
Target lesion revascularization	4
Target vessel revascularization	4
Definite/probable stent thrombosis	0
Cardiac death or MI	3
MACE (cardiac death, MI, CABG or TLR)	8
Device/PCI strategy-related MACE[c]	8

Data are expressed in numbers and percentages. MI, myocardial infarction; CABG, coronary artery bypass grafting; TLR, target lesion revascularisation.

[a]Refers to number of lesions requiring extra stent apart from the Tryton stent and the main vessel stent.

[b]Data expressed in actual numbers which is also equivalent to percentages.

[c]Excludes one patient with a MI at follow up in a territory other than that supplied by treated vessel and another who died of cardiogenic shock that commenced prior to index intervention.

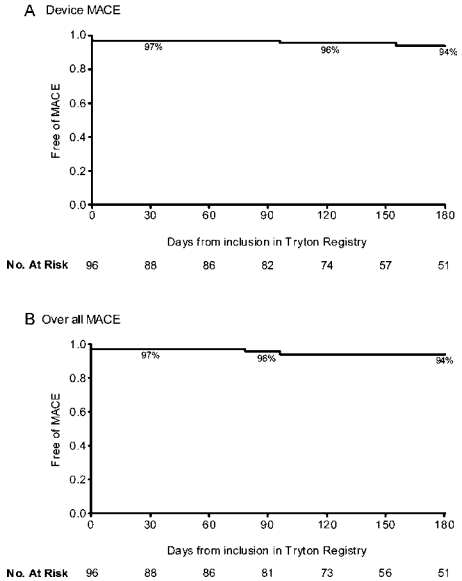

Fig. 3. Kaplan Meier curves for cumulative MACE. A: Composite of index bifurcation treatment-related cardiac death, myocardial infarction, and target lesion revascularization. B: Composite endpoint of all cause mortality, cardiac death, any myocardial infarction, or target vessel revascularization.

The culotte technique seems to be the safest, most effective, offering the best long term outcome of the two stent techniques [9,13–15]. Table VI lists the studies that employed the culotte technique in the DES era. A recent randomized study comparing the culotte technique ($n = 215$) and the crush technique ($n = 209$) found significant differences in biomarker release (8.8 % vs. 15.5%) peri-procedurally favoring the culotte technique though the incidence of major adverse cardiac events including stent thrombosis at six months was similar between the two groups. By eliminating the need for crushing the side branch stent, theoretically trauma to the bifurcation vessel walls is reduced as may be the procedural complications. In the same study, at eight months, angiographic follow-up revealed a significantly higher in-stent restenosis in the "crush" group (10.5% vs. 4.5%). This can be explained by the better scaffolding of the sidebranch ostium. Also recross into the sidebranch is theoretically easier in the culotte group with the guide wire having to cross less layers of struts so that final kissing balloon is more likely to be feasible. This last together with the fewer overlapping layers of metal is thought to reduce the chance of incomplete stent apposition which can then lead to complications such as stent thrombosis and restenosis.

In this all comer study, we have noticed similar rates of procedural success as in the FIM trial reported by our group [5]. The 94% rate in this study was slightly lower than that reported in a culotte versus T stenting study [9]. One explanation could be the difference in scaffolding and recoil properties between the transition zone part of the Tryton stent and a standard stent utilised in the conventional culotte technique. In fact the

TABLE VI. Studies With "Culotte" Technique for Bifurcation Lesions in the Drug Eluting Stent Era

	Culotte-treated patient	Stent used	Kissing %	Follow-up in months	TLR	Binary restenosis rate[a]	Late loss (mm) MV[a]	Late loss (mm) SB	ST	MACE
Hoye et al.	23	SES, PES	74%	8	5%	18.8%; 12.5%	0.48 ± 0.56	0.53 ± 0.33	0%	15.4%
Kaplan et al.	45	SES, PES	84.4%	9	8.9%	6.6%; 4.4%	0.23 ± 0.52; 0.42 ± 0.61	0.28 ± 0.45	2.2%	13.3%
Adriaenssens et al.	134	SES, PES	62%	12	21%	9.1%; 16%	0.10 (−0.04–0.38); 0.34 (−0.03–0.66)	0.30 (−0.01–0.72)	1.5%	26%
Erglis et al.	215	SES, PES	92%	6	2.8%	6.6%; 4.5%	0.12 ± 0.42; 0.19 ± 0.49	0.20 ± 0.48	1.9%	3.7%
Onuma et al.	30	Tryton + SES, PES, EES	100%	6	0%	0%	0.25 ± 0.43; 0.00 ± 0.31	0.17 ± 0.35	0%	9.9%

MV, main vessel; SB, side branch; ST, stent thrombosis; MACE, major adverse cardiac events; SES, sirolimus eluting stents; PES, paclitaxel eluting stents; EES, everolimus eluting stents

[a]First figures indicate value for proximal MV and second figures indicate value for distal MV.

three patients with residual diameter stenosis (%DS) of >30% after successful Tryton stent implantation, had their MLD located at the sidebranch ostium. The clinical importance of this is however uncertain as there was still a significant acute gain in the side branch and none of these patients had a TLR during follow-up. Moreover as Koo et al. demonstrated, QCA is unreliable to assess the functional significance of sidebranch jailing when compared to fractional flow reserve [16]. Of the four cases of TLR, two occurred in the SB covered by the BMS. While we know that the late lumen loss in side branch at six months averaged 0.17 mm in the FIM, being even better than that reported for DES (0.34–0.53 mm) the TLR rate is less than that reported for two stent techniques. Studies report TLR rates of 24–43% the when two BMS stents are employed and 5.1–28% when two DES are used.[1,9-15,17]

Importantly, we did not observe any stent thrombosis in our cohort at six months follow-up which compares well with previous studies that employed the culotte technique. Adriaenssens et al. reports a 1.5% ST rate at 12 months follow-up in a study with 134 lesions in 132 patients. The high rate of final kissing that aims to ensure adequate strut apposition may be a contributing factor.

Although general evidence supports the use of simple, single stenting with conventional stents, the use of dedicated bifurcation stents especially in cases with significantly narrowed true bifurcations where double stenting is highly likely to be performed is probably justified. More data is therefore needed from the registries and randomized trials of the use of dedicated bifurcation stents in this high risk patient/lesion subset.

Study Limitations

This study has the intrinsic limitations of a registry. Selection bias could have occurred in treatment of bifurcation lesions with the study stent. No control group was used to compare the use of this dedicated bifurcation stent and stenting strategy with other devices and techniques. The registry was confined to two academic referral centers and the study lesions were limited to 100. Also, the patients enrolled had no angiographic or other invasive imaging follow-up. However the study still very likely represents the utilization of the Tryton sidebranch stent and its performance in the "real world" everyday practice.

CONCLUSIONS

In a real world, two centre registry, the use of the Tryton Sidebranch stent is associated with good procedural safety and angiographic success rate and acceptable outcome at six months of follow-up.

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7.3

Acute procedural and six-month clinical outcome in patients treated with a dedicated bifurcation stent for left main stem disease: the TRYTON LM multicentre registry.

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Acute procedural and six-month clinical outcome in patients treated with a dedicated bifurcation stent for left main stem disease: the TRYTON LM multicentre registry

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KEYWORDS

- 3-D quantitative coronary angiography
- dedicated bifurcation stents
- left main stem bifurcation
- procedural success
- six-month MACE

Abstract

Aims: Tryton side branch (SB) reverse culotte stenting has been employed for the treatment of left main (LM) stem bifurcations in patients at high risk for bypass surgery. The aim of this study was to assess acute angiographic results and six-month clinical outcome after implantation of the Tryton stent in the LM.

Methods and results: We studied 52 consecutive patients with LM disease treated in nine European centres. Angiographic and clinical data analysis was performed centrally. Fifty-one of 52 patients (age 68±11 yrs, 75% male, 42% unstable angina, SYNTAX score 20±8) were successfully treated with the Tryton stent. Medina class was 1,1,1 in 33 (63%), 1,0,1 in 7 (13%), 1,1,0 in 3 (6%), 0,1,1 in 8 (4%) and 0,0,1 in 1 (2%). The Tryton stent on a stepped balloon (diameter 3.5-2.5 mm) was used in 41/51 (80%) of cases. The mean main vessel stent diameter was 3.4±0.4 mm with an everolimus-eluting stent employed in 30/51 (59%) of cases. Final kissing balloon dilatation was performed in 48/51 (94%). Acute gain was 1.52±0.86 mm in the LM and 0.92±0.47 mm in the SB. The angiographic success rate was 100%; the procedural success rate reached 94%. Periprocedural MI occurred in three patients. At six-month follow-up, the TLR rate was 12%, MI 10% and cardiac death 2%. The hierarchical MACE rate at six months was 22%. No cases of definite stent thrombosis occurred.

Conclusions: The use of the Tryton stent for treatment of LM bifurcation disease in combination with a conventional drug-eluting stent is feasible and achieves an optimal angiographic result. Safety of the procedure and six-month outcome are acceptable in this high-risk lesion PCI. Further safety and efficacy studies with long-term outcome assessment of this strategy are warranted.

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Introduction

Stenting of the left main (LM) stem is increasingly recognised as a valid revascularisation strategy in patients with significant disease involving this important segment of the coronary tree. Although coronary artery bypass surgery (CABG) is considered a superior treatment option for LM disease, some patient subgroups may still benefit from revascularisation by PCI. Randomised trials of LM PCI versus CABG have repeatedly revealed target vessel revascularisation (TVR) as the Achilles heel of the former[1]. However, recent studies have shown that patients with less diffuse coronary disease in low SYNTAX score tertiles have comparable outcomes with PCI and CABG[2]. Having secured at least a similar safety profile, PCI of LM stenosis has been upgraded to a class IIa or IIb indication in the current European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American College of Cardiology/American Heart Association practice guidelines[3,4].

Not all LM lesions have similar outcomes and, in fact, involvement of the LM bifurcation is associated with suboptimal short-term and long-term results when conventional stents are employed. Poor angiographic results are often obtained with the use of a provisional stenting technique in cases where the side branch (SB) is significantly diseased. Refinement of interventional techniques and the introduction of dedicated devices may improve the outcome of LM PCI. The use of a dedicated bifurcation stent – the Tryton side branch stent in conjunction with a conventional stent in a "reverse culotte" technique – facilitates stenting and may potentially improve angiographic results and clinical outcome in patients who undergo LM bifurcation intervention. Indeed, use of this dedicated stent has been increasing in the "real world" even in "off-label" anatomic locations, including the LM bifurcation[5].

The aim of the present study was to assess the acute angiographic outcome of LM bifurcation treatment with the Tryton stent (Tryton Medical, Inc., Durham, NC, USA) in conjunction with a conventional stent. The acute and mid-term clinical outcome up to six months was also investigated.

Methods

The Tryton LM registry was established by retrospective inclusion of patients treated in nine European centres by very experienced operators. Procedural and clinical data of all consecutive patients in whom treatment of the LM with a Tryton stent was attempted were collected on a purposely designed electronic case report form (CRF), which was sent to the investigators. The investigators at each centre (see authors) were responsible for filling in the forms and vouch for the integrity of the data provided centrally for analysis. Angiography films of the procedures and follow-up angiograms (when available) were collected centrally and analysed by three experienced interventional cardiologists (MM, CG, RJvG).

In this report, we present the data of the first 52 patients with LM bifurcation disease in whom the operators intended to use the Tryton stenting technique. The inclusion period spanned May 2008 to October 2011.

Prespecified primary endpoints of the study included acute gain in the three segments of the bifurcation as measured by quantitative coronary angiography (QCA) as well as procedural and six-month clinical outcome in terms of major adverse cardiac events (MACE).

Patient population

Patients included were selected by the operators and, whenever feasible, after case discussion by a heart team. In general, patients were either unfit for surgery, had previous bypass surgery, had isolated LM with low SYNTAX scores or presented as an emergency. The size of the Tryton stent available at the time of patient enrolment limited the range of vessel sizes that could be treated. The visually estimated reference diameter of the main vessel (MV) could be 2.5-5.0 mm and that of the SB in the range 2.5-2.75 mm. Also, the LM had to be ≥7 mm in length to allow an adequate landing zone of the proximal part of the stent. However, the decision to treat the bifurcation and employ a Tryton stent remained at the discretion of the treating interventional cardiologist.

Device description and deployment sequence

The Tryton stent is a balloon-expandable cobalt chromium stent with strut thickness of 84 µm. The stent is available in one standard length of 19 mm and has three distinct zones: a distal SB zone, which is 6.5 mm long, a central transition zone 4.5 mm in length, and a proximal MV zone of 8 mm. The distal zone has a standard slotted tube workhorse stent design; the central transition zone consists of three panels, while the proximal MV zone is composed of three fronds that terminate proximally in two circumferential bands (only one in the first-generation device). The stent is mounted either on a balloon with uniform diameter (straight type) or on a stepped balloon (tapered type). Stent sizes (proximal-distal) available during the study period were 2.5-2.5; 3.0-2.5; 3.5-2.5 and 3.5-3.0. The stent delivery system has four markers to delineate the proximal and distal ends of the stent as well as the proximal and distal parts of the transition zone. After optional wiring of both MV and SB for predilation, the Tryton stent is advanced over the wire into the SB and is positioned with the guidance of the two middle markers which should straddle the carina. Deployment of the stent is followed by retraction of the guidewire from the SB and repositioning it through the fronds of the transition zone into the distal MV. A standard stent is then advanced, positioned, and deployed in the MV, jailing the stented SB. Proximal optimisation technique can be employed at this time by inflating a balloon the size of the proximal MV with the distal marker at the ostium of the SB. This may facilitate wire recross into the SB for final kissing balloon (FKB) dilation. A case example is presented in **Figure 1**. Further details of the Tryton stent and deployment procedure have been described in detail elsewhere[6].

Procedure

Patients were pretreated with aspirin and clopidogrel. Intravenous heparin was administered to maintain an activated clotting time of >250 seconds. Glycoprotein IIb/IIIa inhibitor use was left to the discretion of the treating interventional cardiologist. Delivery

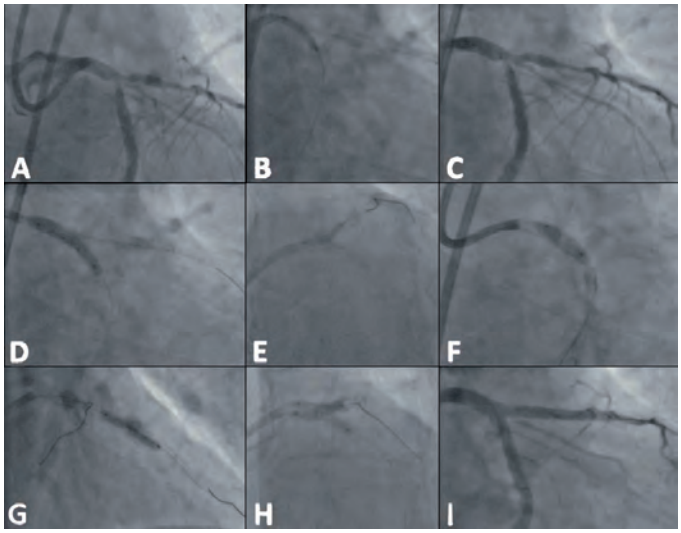

Figure 1. *Implantation sequence of the Tryton stent in the left main stem bifurcation. This 78-year-old man was deemed high risk for surgery when he presented with unstable angina pectoris. The left main (LM) stem showed a Medina class 1,1,1 bifurcation lesion and further disease in segment 6 (A). The left anterior descending (LAD) and left circumflex (LCx) coronary arteries were wired and the latter was predilated with a 2.5 mm balloon (B). A 3.5-2.5×19 mm Tryton stent was positioned with the middle markers straddling the carina (C) and subsequently implanted by inflating the stepped balloon (D). The LCx wire was then retracted to the point of bifurcation and redirected into the LAD. After removal of the jailed first LAD wire, the LAD was predilated with a balloon (E) and a 3.5×18 mm XIENCE PRIME™ stent (Abbott Vascular, Redwood City, CA, USA) was placed along the LAD and across the LCx (F). After implantation of the stent, a second overlapping stent was used to treat the stenosis in segment 6 (G). The LCx was then rewired and final kissing balloon inflations were performed (H) with a good angiographic result (I).*

failures, need for additional overlapping stents to cover the whole lesion, additional balloon dilation and procedural angiographic and clinical complications were noted. Aspirin was prescribed indefinitely while clopidogrel was prescribed for at least 12 months after the index procedure.

Clinical follow-up

In-hospital events were recorded in the patient's clinical notes. Clinical follow-up was obtained by clinical visits or phone interview during which data on hospital readmission and MACE were collected. Medical records, discharge summaries and any repeat angiography films of patients with suspected events were systematically reviewed and adjudicated by local cardiologists according to established criteria defined below.

Definitions

Device success was defined as successful deployment of the intended stent without system failure. Angiographic success was defined as <30% residual stenosis and TIMI 3 flow in both MV and SB after the procedure. Procedure success included angiographic success in the absence of in-hospital MACE, defined as a composite of cardiac death, myocardial infarction (MI) and ischaemia-driven TVR. MI was defined as clinical signs of acute ischaemia, associated with a CK-MB mass or troponin-T/troponin-I increase to ≥3 times the upper limit of normal and corresponding changes on a 12-lead electrocardiogram (ECG). TVR was defined as revascularisation of any part of the index coronary artery. Definite stent thrombosis was defined according to the Academic Research Consortium (ARC) definitions[7].

Angiographic analysis

QUANTITATIVE CORONARY ANGIOGRAPHY

QCA was performed with the Cardiovascular Angiography Analysis System (CAAS; Pie Medical Imaging, Maastricht, The Netherlands) version 5.10, by experienced analysts blinded to the clinical data. All available studies were analysed with a dedicated 2-D bifurcation QCA algorithm, using matched projections, pre- and post-procedure, and end-diastolic frames. The vessel distal to the LM bifurcation where the distal Tryton stent was implanted was defined as the SB, whereas the vessel where the conventional stent was implanted was identified as the distal main vessel (DMV). A device-oriented analysis

was performed, whereby the region of interest around the LM bifurcation was demarcated according to the stent borders as identified on the positioning/implantation cine runs. Specifically, the Tryton stent proximal and distal edges were defined as the proximal border of the proximal main vessel (PMV) and the distal SB border, respectively, whereas the distal DMV border was set at either the distal edge of the DES implanted through the Tryton stent or at the first major SB distal to the LM bifurcation in case of multiple overlapping stents. The minimal lumen diameter (MLD), reference vessel diameter (RVD) and percent diameter stenosis (DS) were quantified for the stented vessel segments and 5 mm peri-stent segments. Respective values for corresponding stent and segment were obtained from the six-segment bifurcation model (segments 1 and 2 for PMV, 3 and 4 for DMV, 5 and 6 for SB)[8]; in addition, quantitative parameters for 3 mm ostial segments were derived from the 11-segment bifurcation model (segment 11 and 8 for DMV and SB, respectively) **(Figure 2** and **Figure 3)**. Reference vessel obstruction analysis was performed with either the automatic (interpolation) method or local reference method (single point for each vessel segment). The second method was mostly reserved for diffusely diseased vessel segments prior to treatment[9]. Finally, proximal and distal bifurcation angle (BA) values were calculated.

In the cases where at least two angiographic images of the LM bifurcation separated by a viewing angle of ≥30° were available for both pre- and post-procedure, a 3-D reconstruction was also performed with a dedicated bifurcation algorithm[10]. Specifically, 2-D analysis was performed first using the 2-D angiographic image showing the best (optimal) view of the LM bifurcation. After saving the 2-D analysis results (numerical values and graphs) the vessel contours of this optimal view were imported into the 3-D analysis algorithm together with the second 2-D image, which still required contouring following the procedure already described. In the 3-D reconstructed image, segmentation of the region of interest and reporting of angiographic quantitative parameters were analogous with the 2-D analysis; thereby results from 2-D and 3-D analyses were directly comparable.

The depth of implantation of the Tryton stent was measured by QCA using the two middle markers as illustrated in **Figure 4**. The angiography film showing the positioning of the stent prior to implantation was analysed for all but 11 cases in which this was not recorded. The distances between the proximal middle marker and the carina and the distal middle marker and the carina were measured. A difference of ≥1 mm between the two measurements was identified as inappropriate implantation.

SYNTAX SCORE

SYNTAX score was calculated by an experienced analyst as previously described using the programme on the website www.syntaxscore.com[11].

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±SD or as median (interquartile ranges) whereas dichotomous data are summarised as counts

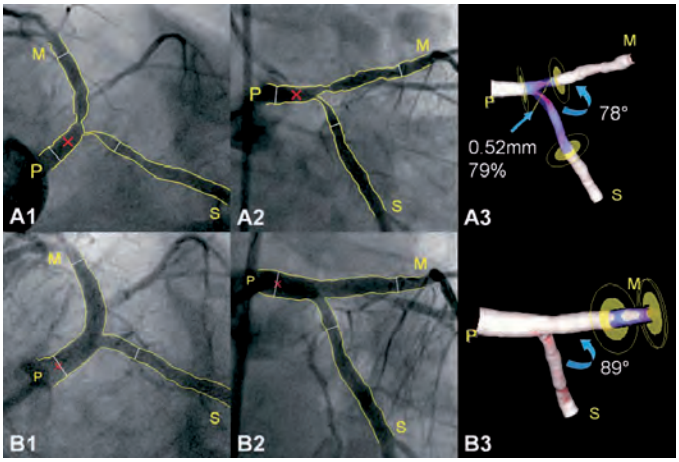

Figure 2. *Three-dimensional reconstruction pre- and post-procedure. A1-A2: A left and a right anterior oblique caudal view of a left main (0,1,1) bifurcation lesion are shown before stent placement; a Tryton stent will be placed from the proximal main vessel (P) into the side branch (S). Thin white lines demarcate the region of interest, whereas the red cross marks the common image point facilitating the 3-D reconstruction (A3); the most severe stenosis is located in the side branch ostium. B1-B3: Respective images post-procedure. Stenosis around the bifurcation is reduced, whereas minor obstruction is now located distal to the drug-eluting stent in the distal main vessel (M); PCI resulted in a slight increase in the 3-D distal bifurcation angle.*

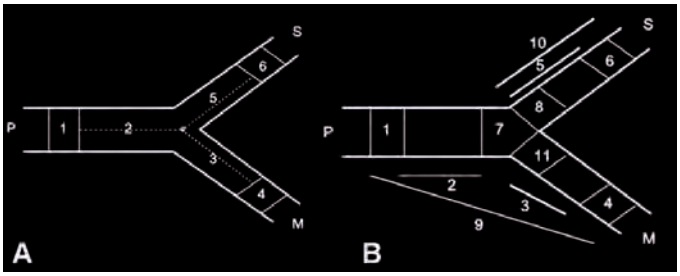

Figure 3. *Bifurcation segment models in the Cardiovascular Angiography Analysis System (CAAS). Segments 2, 3 and 5 in both models reflect the segments where the stents were placed in the proximal main vessel (P), distal main vessel (M) and side branch (S), respectively; segments 1, 4 and 6 are corresponding 5 mm-long peri-stent segments. Segments 8 and 11 in the extended model (B) reflect 3 mm-long ostial segments for the side branch and distal main vessel, respectively.*

and/or percentages. The paired t-test was employed for comparisons of quantitative parameters pre- and post-procedure and between 2-D and 3-D estimates of the same parameters. Statistical analysis was performed using SPSS software version 20 (SPSS, Chicago, IL, USA).

Results

Fifty-two LM bifurcation lesions were included in the TRYTON LM registry between May 2008 and October 2011. **Table 1** shows the baseline characteristics of the study cohort. The mean age of patients was 68.3±10.8 years and 75% were male. Fifty-eight percent of patients presented for PCI with stable angina while 25% presented with a myocardial infarction and 8% were in cardiogenic shock.

Coronary lesion characteristics are summarised in **Table 1**. The average SYNTAX score was 20±8 and 19% of patients had a previous CABG. Five patients had two bifurcation lesions that needed revascularisation. Eighty-five percent of lesions were true bifurcation lesions (1,0,1 or 1,1,1 or 0,1,1) .

The mean reference diameters for the LM stem, DMB and SB were 4.00, 2.63 and 2.48 mm, respectively. The mean DS was 39.5%, 36.2% and 41.8% for LM, DMB and SB, respectively. The mean angle between the LM and the SB was 139.4˚, while that between the DMB and the SB was 78.5˚.

All stents implanted during the procedure except for the Tryton stent were drug-eluting. Failure of delivery of the Tryton stent occurred in one patient despite repeated predilatation of a heavily calcified LM and a very tight lesion of the left circumflex (LCx) coronary artery. Eventually, a conventional drug-eluting stent (DES) was placed with a good angiographic result. For the rest of the cohort, a Tryton stent on a stepped balloon with a diameter of 3.5-2.5 mm was successfully deployed in 41/51 (80%) cases. In 11/51 (22%) cases, the distal zone of the Tryton stent was implanted in the left anterior descending (LAD) coronary artery. Six (55%) of these cases were protected by a left internal mammary artery. For the remaining five (45%), the LCx was larger in diameter than the LAD and the operator chose the latter as the "side branch". The mean MV stent diameter

Table 1. Baseline clinical and angiographic characteristics.

Baseline clinical characteristics	n=52
Age, years	68.3±10.8
Male sex	75% (39)
Hypertension	60% (31)
Diabetes	38% (20)
Hypercholesterolaemia	58% (30)
Current smoker	17% (9)
Family history of coronary artery disease	30% (16)
End stage renal failure	2% (1)
Previous percutaneous coronary intervention	35% (18)
Previous coronary artery bypass surgery	19% (10)
History of myocardial infarction	29% (15)
Clinical presentation	
Stable angina	58% (30)
Unstable angina	17% (9)
ST-segment myocardial infarction	2% (1)
Non-ST-segment myocardial infarction	23% (12)
Cardiogenic shock	8% (4)
Angiographic characteristics	
SYNTAX score	20±8
Left main stem bifurcation	
MEDINA classification	
1,1,1	63% (33)
1,1,0	6% (3)
1,0,1	13% (7)
1,0,0	0% (0)
0,1,1	8% (4)
0,0,1	2% (1)
0,1,0	0% (0)
Functional LIMA on LAD	19% (10)

LAD: left anterior descending coronary artery; LIMA: left internal mammary artery graft

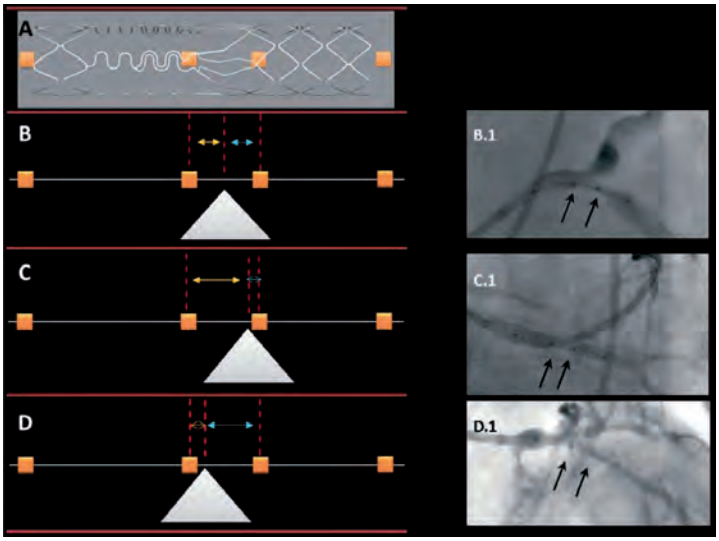

Figure 4. *Depth of implantation assessement. The Tryton stent delivery system has four markers (depicted in orange boxes): the outer markers delineate the proximal and distal ends of the stent, while the two middle markers delineate the transition zone (A). The two middle markers (black arrows on angiographic images) should straddle the carina (white triangle) during implantation. Equal distances between the proximal middle marker (yellow arrow) and the distal middle marker (blue arrow) to a line perpendicular to the carina indicate appropriate implantation depth as exemplified in B and B.1. The implantation in C and C.1 is not deep enough (yellow>blue arrow), while that in D and D.1 is too deep (yellow<blue).*

was 3.4±0.4 mm with an everolimus-eluting stent employed in 30/51 (59%) of cases. FKB dilatation was performed in 48/51 (94%) bifurcation lesions. **Table 2** summarises procedural parameters.

There were no device-related complications except for one delivery failure. Thus, the device success rate was 98%. Angiographic success was achieved in all patients (100%). One patient had a non-flow-limiting dissection in the LAD following deployment of a MV conventional stent that was used in combination with the Tryton stent for treatment of a LAD/diagonal branch bifurcation lesion. The dissection at the proximal edge of the stent was covered by placement of an additional stent and the operator went on to treat the LM bifurcation with a second Tryton stent, achieving a good result. The patient had no evidence of periprocedural infarction. A second patient also had two Tryton stents deployed to treat two bifurcation lesions during the same procedure with a good result. In total, three patients developed periprocedural MI without angiographic complications so that procedural success reached 94%.

Table 2. Procedural characteristics.

Characteristics	
Tryton implanted in LAD	22% (11/51)
Tryton implanted in intermediate artery	2% (1/51)
Main vessel stent size	
Diameter, mm	3.4±0.4
Length, mm	22.9±4.9
Main vessel stent type	
Everolimus-eluting	59% (30/51)
Biolimus-eluting	14% (7/51)
Zotarolimus-eluting	8% (4/51)
Other DES	19% (10/51)
Additional stent in the side branch	15/49 (30%)
Additional stent in the main vessel	13/49 (27%)
Final kissing balloons	94% (48/51)
Device success	51/52 (98%)
Procedural success	49/52 (94%)

DES: drug-eluting stents; LAD: left anterior descending coronary artery

QCA RESULTS

Two-dimensional analysis was performed in 46 cases. The other cases had to be excluded due to inadequate cineangiography either pre- or post-procedure (no clear view of the bifurcation, overlapping vessel segments, presence of angiographic guidewires). Results for diameter-derived parameters for the overall 2-D analysis are shown in **Table 3A**. Acute gain in the LM and in the SB was 1.52±0.86 mm and 0.92±0.47 mm, respectively.

Three-dimensional analysis was feasible in 14 cases and results for diameter-derived parameters are shown in **Table 3B**. On average, two-dimensional BA values were larger as compared to the

3-D ones, both pre- and post-procedure **(Table 4)**. However, the difference was significant for pre-PCI proximal BA values (145.1° vs. 132.4°, p=0.03) only.

From the 46 angiography films analysed with 2-D QCA, the proximal BA changed by ≥5° in 65% (28/43) of cases, while the distal BA changed by more than ≥5° in 74% (32/43) of cases. For the distal BA, most cases with a change showed a narrowing of the angle and this occurred in 54% of the QCA cohort. On the other hand, the proximal BA most commonly widened (40% of cases) or remained the same (35%).

Depth of implantation of the Tryton stent was assessable in 77% (40/52) of cases. Depth was deemed appropriate in 38% (15/40). In 43% (17/40) of those assessed, the implantation was not deep enough, while in 20% (8/40) implantation was too deep. These results are summarised in **Table 5**.

Table 3A. 2-D QCA analysis of left main bifurcation pre- and post-procedure (n=43).

	Pre-procedure			Post-procedure				
	In-stent			In-stent				
	MLD (mm)	RVD (mm)	DS (%)	MLD (mm)	RVD (mm)	DS (%)	Acute gain	*p*-value
PMV	2.42±0.98	4.00±0.77	39.5±20.2	3.94±0.75	4.50±0.82	11.9±9.9	1.52±0.86	<0.0001
DMV	1.67±0.51	2.63±0.43	36.2±17.6	2.75±0.41	3.26±0.43	15.5±8.9	1.07±0.58	<0.0001
SB	1.44±0.51	2.48±0.46	41.8±18.7	2.35±0.39	2.83±0.42	16.6±9.0	0.92±0.47	<0.0001
Tryton stent	1.62±0.78	3.34±0.90	51.7±17.5	2.78±0.86	3.51±1.14	20.1±8.7	1.16±0.97	<0.0001
Ostial DMV	1.91±0.64	2.68±0.43	28.6±19.3	3.06±0.53	3.33±0.42	8.3±9.1	0.87±0.56	<0.0001
Ostial SB	1.58±0.61	2.48±0.44	36.1±21.4	2.46±0.42	2.84±0.42	13.2±9.9	1.15±0.58	<0.0001
	In-segment			In-segment				
	MLD (mm)	RVD (mm)	DS (%)	MLD (mm)	RVD (mm)	DS (%)	Acute gain	*p*-value
PMV	2.42±0.98	4.00±0.77	39.5±20.2	3.86±0.65	4.49±0.82	13.5±8.8	1.43±0.80	<0.0001
DMV	1.65±0.50	2.62±0.43	36.9±16.9	2.52±0.48	3.26±0.45	22.6±10.8	0.87±0.53	<0.0001
SB	1.41±0.51	2.48±0.46	42.8±18.4	2.15±0.44	2.81±0.42	23.6±11.1	0.74±0.52	<0.0001
Tryton stent	1.62±0.78	3.34±0.90	51.7±17.5	2.42±0.83	3.25±1.04	25.6±10.3	0.79±0.99	<0.0001
Ostial DMV	N/A			N/A			N/A	
Ostial SB	N/A			N/A			N/A	

2-D: two-dimensional; DMV: distal main vessel; DS: percent diameter stenosis; MLD: minimal lumen diameter; N/A: non-applicable; PMV: proximal main vessel; QCA: quantitative coronary angiography; RVD: reference vessel diameter; SB: side branch

Table 3B. 2-D and 3-D QCA analysis of left main bifurcation pre- and post-procedure in 3-D analysable cases (n=14).

	Pre-procedure in-stent					
	2-D			3-D		
	MLD	RVD	DS	MLD	RVD	DS
PMV	2.61±1.08	4.05±0.73	36.41±20.72	2.82±0.99	3.83±0.67*	26.55±20.75**
DMV	1.55±0.49	2.48±0.30	37.19±18.88	1.61±0.63	2.54±0.38	37.39±18.25
SB	1.31±0.41	2.46±0.44	45.93±17.75	1.41±0.49	2.41±0.54	41.22±18.21
Tryton	1.38±0.48	3.13±0.70	55.77±12.70	1.45±0.56	2.84±0.85	48.17±15.46**
Ostial DMV	1.72±0.61	2.52±0.29	31.82±21.25	1.81±0.70	2.54±0.40	29.36±20.52
Ostial SB	1.44±0.55	2.45±0.43	40.77±22.94	1.54±0.62	2.40±0.53	35.96±23.33*
	Post-procedure in-stent					
	2-D			3-D		
	MLD	RVD	DS	MLD	RVD	DS
PMV	3.99±0.73	4.51±0.67	11.41±9.41	4.13±0.70	4.52±0.70	8.55±6.78
DMV	2.82±0.48	3.30±0.42	14.51±8.17	2.83±0.45	3.29±0.38	14.15±7.20
SB	2.38±0.39	2.86±0.50	16.70±6.86	2.42±0.35	2.78±0.46	12.55±4.82*
Tryton	2.83±0.87	3.53±1.15	19.38±6.03	2.60±0.55	3.04±0.71	13.95±4.51**
Ostial DMV	3.09±0.46	3.33±0.37	7.27±8.45	3.14±0.48	3.35±0.41	6.53±6.93
Ostial SB	2.49±0.46	2.87±0.50	13.12±8.29	2.56±0.47	2.82±0.50	9.06±7.30

2/3-D: two/three-dimensional; DMV: distal main vessel; DS: percent diameter stenosis; MLD: minimal lumen diameter; PMV: proximal main vessel; QCA: quantitative coronary angiography; RVD: reference vessel diameter; SB: side branch; *p≤0.05 compared to 2-D; ** p≤0.01 compared to 2-D

Table 4. Bifurcation angles pre and post Tryton implantation.

	Preprocedural		Postprocedural					
	LM-SB	DMB-SB	LM-SB	Angle change	*p*-value	DMB-SB	Angle change	*p*-value
2-D QCA (n=43)	139.4±34.7	78.5±32.7	142.8±29.2	3.4±18.8	0.24	75.2±27.1	–3.39±24.0	0.36
3-D QCA (n=14)	132.4±15.0	65.5±18.7	134.0±17.5	1.58±11.5	0.62	65.7±16.8	0.19±19.6	0.97

Table 5. Depth of implantation.

Tryton implantation parameters	
Tryton successfully implanted	98% (51/52)
Implantation depth assessable	77% (40/51)
Proximal middle marker to carina distance, mm	3.11±1.85
Distal middle marker to carina distance, mm	1.35±1.87
Appropriate implantation	38% (15/40)
Implantation too deep	20% (8/40)
Implantation not deep enough	43% (17/40)

CLINICAL FOLLOW-UP

At a median of six months, one patient of the entire cohort treated with the Tryton stent was lost to follow-up. The events in the rest as well as the hierarchical MACE are reported in **Table 6**. One patient died of cardiovascular complications at 83 days after the index procedure. Two other patients died of non-cardiac causes, one from septic shock and the other from a gastrointestinal bleed. Apart from the three periprocedural MIs, two other patients suffered a NSTEMI at 55 days and 92 days post procedure, respectively. In the first patient, angiography revealed no obvious restenosis or culprit lesion, whereas in the second restenosis with a hazy lesion in the SB ostium was treated with balloon angioplasty. In total, six patients had TVR, all involving the SB, with one of them being referred for CABG because of concomitant MV and SB restenosis. All cases of TVR occurred in the side branch with QCA-derived reference diameter of <2.3 mm. The depth of implantation in cases of TVR was appropriate in two, too deep in two and not deep enough in two.

On further analysis of the baseline and follow-up angiography films of cases with restenosis, the following observations were made: all cases of restenosis involved the SB ostium. Evaluation of procedural steps revealed prolonged attempts at rewiring of the SB for FKB.

No cases of definite stent thrombosis were reported.

Table 6. Acute and 6-month clinical outcome.

Periprocedural adverse events	
Procedure-related MI	6% (3/50)
Target vessel revascularisation	0 (0/50)
ARC definite stent thrombosis	0 (0/50)
Cardiac death	0 (0/50)
MACE (hierarchical)	6% (3/50)
30-day adverse events	
Myocardial infarction	6% (3/50)
Target vessel revascularisation	0% (0/50)
ARC definite stent thrombosis	0% (0/50)
All-cause death	4% (2/50)
Cardiac death	0% (0/50)
MACE (hierarchical)	6% (3/50)
6-month adverse events	
Myocardial infarction	10% (5/50)
Target vessel revascularisation	12% (6/50)
Main vessel	12% (6/50)
Side branch	2% (1/50)
ARC definite stent thrombosis	0% (0/50)
All-cause death	6% (3/50)
Cardiac death	2% (1/50)
MACE (hierarchical)	22% (11/50)

Discussion

Use of the Tryton side branch stent for treatment of LM bifurcation lesions was associated with a high rate of device and procedural success without complications in such a high-risk patient and lesion cohort. The angiographic result is excellent with optimal acute luminal gain in all three segments of the bifurcation including the distal MB and SB ostia as measured by 2-D and 3-D QCA. Although BA changes were observed to similar extents as previously described for two-stent techniques, they were not associated with adverse events at follow-up. At six months, TLR (12%) was due almost exclusively to SB ostium restenosis, an event that warrants in-depth evaluation.

Previous studies have shown that PCI of the LM has two distinct anatomical subcategories distinguished by their differential outcome in terms of restenosis. In fact, while treatment of disease limited to the shaft compares well with CABG results, that of the bifurcation is limited by excessive revascularisation rates. A LM substudy from the j-Cypher Registry found a three-year TVR rate of 3.6% for ostial lesions and significantly higher rates (17.1%) after bifurcation stenting with early-generation sirolimus-eluting stents[12]. Two-stent strategies including crush, culotte and T stenting provide better angiographic results at the expense of a more complex procedure with higher risk of complications and lack of superiority or even inferiority in terms of efficacy when compared to provisional T stenting. Reports of a 30.9% TVR rate at three years with two-stent techniques compared with a more acceptable 11.1% for provisional stenting are a matter of some concern[12]. An Italian survey also reported similar

rates at two years with a similar difference between simple and more complex techniques (TLR-free survival 87% vs. 73%)[13]. Such trends are maintained up to five-year follow-up[14]. It is worth noting that the majority of two-stent techniques employed in these studies were crush and T stenting with under-representation of culotte stenting. The latter has the potential advantage of a better scaffolding of the distal vessel ostia and at the same time may minimise the number of unopposed struts at the bifurcation. In true bifurcation lesions with significant SB involvement, these features may be particularly advantageous. The Tryton stent facilitates the reverse culotte technique and, as shown in previous reports, it simplifies the interventional technique leading to a low intraprocedural complication rate and excellent angiographic results. In our current registry, these theoretical advantages still resulted in a TLR rate of 12% at six months. Some important device-dependent and operator-dependent features have to be considered in order to understand how these may interact to affect clinical outcome.

DEPTH OF IMPLANTATION

The middle markers on the Tryton stent delivery system are essential to guide the desired depth of implantation of the device. Straddling the carina between the two markers allows correct positioning of the stent transition zone, resulting in good scaffolding of the SB ostium. This zone has a lower radial strength than the SB zone due to the design, which on the other hand allows for easier recross of wires, balloons and stents across it and along the MV. Therefore, a balance has to be sought, as implanting the device too deep will result in poor SB ostial scaffolding while too shallow an implantation will result in difficult MV rewiring. Most operators in our series preferred to keep the major part of the transition zone in the MV. This strategy probably provides better scaffolding of the SB ostium, while recrossing into the relatively large MV was not associated with any significant difficulty. Theoretically, this issue would be best explored with the use of intraprocedural intravascular ultrasound (IVUS) or optical coherence tomography (OCT). However, it should be noted that inappropriate implantation depth was not predictive of restenosis up to six months post procedure.

STENT SIZING

Small branch vessels treated with the Tryton stent were more likely to have restenoses at follow-up. Indeed, five of the seven cases with restenosis at six months occurred in vessels less than 2 mm by QCA. Introduction of a drug-eluting version of the Tryton stent may potentially overcome this problem in vessels ≤2.5 mm in diameter.

CHANGE IN BIFURCATION ANGLE AFTER TRYTON-CONVENTIONAL STENT IMPLANTATION

Cardiac motion may change BA, namely widening the angle between the LM and the LCx, and simultaneously narrowing the angle between the LAD and the LCx by about 8°[15]. PCI of the LM bifurcation also changes the angle in most instances, narrowing it by about 5°. Our study showed similar changes with the use of a dedicated bifurcation stent.

In a recent 3-D QCA study, a change of ≥5° between either the PMB and SB or DMB and SB after stenting was considered significant. Of the 102 bifurcations included in the study, 15 involved the LM. The angle between the DMB and SB changed significantly. Of note, the angle became wider with the use of complex as compared to simple bifurcation stenting techniques. However, this was not associated with adverse events. On the other hand, widening of the angle between the PMB and SB was associated with fewer events, while angle narrowing resulted in a higher rate of complications[16]. In our study, neither the angle at baseline nor a change in the angle after PCI was associated with adverse events, including restenosis. This, however, does not exclude a higher postulated risk of bifurcation restenosis with very wide angles between the DMB and SB, as scaffolding at the point of bifurcation may be reduced. Such bifurcations are under-represented in our study cohort, reflecting appropriate selection of cases based on the anatomy by the treating interventional cardiologist. Therefore, the impact of bifurcation angle change on outcome in LM intervention in appropriately selected cases certainly remains limited.

OTHER PROCEDURAL CHARACTERISTICS THAT MAY HAVE AN IMPACT ON OUTCOME

Technical strategies to ensure long-term patency include lesion preparation with rotational atherectomy if lesions are significantly calcified, balloon predilatation[17], use of cutting balloons when needed, implantation of stents at relatively high pressures, and post-dilatation with non-compliant balloons. Use of IVUS imaging[18] may be of help in assessing the need for predilatation or atherectomy, in appropriately sizing the vessel, and to evaluate the need for further post-dilatation after stenting in order to ensure good acute luminal gain. In patients undergoing bifurcation lesion PCI, FKB dilation has a positive effect on acute angiographic results, which seems to translate into better clinical outcome[19]. Indeed, the Nordic-Baltic Bifurcation Study III showed that FKB dilation reduced angiographic SB restenosis at six months in bifurcation lesions other than distal LM, especially in patients with true bifurcations (7.9% vs. 15.4% [p=0.039] for all bifurcations and 7.6% vs. 20.0% [p=0.024] for true bifurcations)[20]. Prolonged attempts at rewiring the SB for FKB were noted on detailed analysis of the Tryton cases needing revascularisation at follow-up in the current registry. We can speculate that this may be the result of passage of the wire behind the struts of the SB ostial portion of the Tryton stent (presumably at the transition zone). If that is the case, kissing inflations would crush the transition zone against the ostium, resulting in reduced carina scaffolding despite the optimal acute angiographic result and restenosis. Another possible cause of SB restenosis could be the lack of an antiproliferative drug coating on the Tryton stent implanted in a site at high risk of restenosis, such as the LCx ostium.

QCA FOR BIFURCATION ANALYSIS

The mean values for diameter stenosis established by QCA analysis in the cohort are less than 50% in all three segments of the bifurcation. This implies that such measurements were not used in isolation to

determine whether the LM bifurcation should be treated or not. Discrepancy between eyeballing and QCA (overestimation of eyeballing), use of complimentary parameters such as lesion instability, pressure drop on engagement of the LM and other physiological parameters may have instigated treatment. Angiographic derivation of the reference vessel diameter prior to intervention may underestimate the true lumen diameter, especially in diffusely diseased segments. In fact after stent implantation we observed an enlargement of the RVD. This occurs commonly with the LM since it is an end vessel and involvement starting from the ostium precludes measurement of the true RVD by angiography on the pre-treatment film. Despite these plausible reasons for the low DS in treated LM bifurcations, we still cannot exclude overtreatment, i.e., intervention of apparently non-significant lesions with the interventionalist being keen to treat if there is doubt about the significance as it is the LM.

LIMITATIONS

The present study has the intrinsic limitations of a registry. These cases are selected and therefore may not reflect use in all-comer LM lesions. In particular, the limited Tryton stent sizes available at the time of implantation may have affected the outcome. Therefore, it is more likely that the present results reflect stent performance in the range of vessel sizes treated in our cohort. There was no control group to compare the use of this dedicated bifurcation stent and stenting with other devices and techniques. Moreover, the number of patients enrolled in the registry is too limited to draw conclusions on definite and reproducible clinical outcome rates. Also, the majority of patients enrolled had no angiographic or other invasive imaging follow-up. QCA was not possible in 100% of the cohort for the reasons explained above. The use of intravascular imaging techniques (IVUS or OCT) was not available in the majority of cases and would have been useful for better evaluation of the cases of stent failure.

Conclusions

Use of the Tryton stent for treatment of LM bifurcation disease in combination with a conventional drug-eluting stent is feasible and results in optimal acute angiographic results. Safety of the procedure and six-month clinical outcome are acceptable in this high-risk lesion PCI; further prospective safety and efficacy studies with intravascular imaging as well as long-term outcomes of this strategy are warranted.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Part VIII

- CONCLUSION AND SUMMARY
- SAMENVATTING
- CURRICULUM VITAE
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CONCLUSION AND SUMMARY

The development of drug eluting stents (DES) has brought about an important and significant improvement in terms of efficacy for the percutaneous treatment of coronary artery disease (chapter 1). The inhibition of in-stent neo-intimal hyperplasia resulted in a dramatic decrease in the need for repeat revascularization at one year. This was clearly demonstrated by the pivotal trials and registries comparing the first generation sirolimus eluting stents (SES) and the paclitaxel eluting stents (PES) with bare metal stents (BMS). Longer term data revealed a cumulative increase in the incidence of target vessel revascularization (TVR) in patients treated with DES raising concerns of an eventual catch-up phenomenon. Using data from the established RESEARCH (Rapamycin eluting stent evaluated at Rotterdam Cardiology Hospital) and T SEARCH (Taxus Stent evaluated at Rotterdam Cardiology Hospital) the sustained advantage of SES and PES over BMS is demonstrated at 4 years in patients with stable coronary artery disease (chapter 2). During this follow-up period SES and PES use resulted in a 50% reduction in TVR procedures and thereby a 34% decrease in major adverse cardiac event rates (MACE) when compared to BMS use. A trend towards a higher incidence of very late stent thrombosis with DES in our 4 year report became statistically significant with more events occurring in a wider, 'all-comer' study report at even longer term follow-up of 6 years (chapter 3). Notably almost half of the patients treated in this study cohort presented with unstable coronary syndromes and around 20% were treated for an acute myocardial infarction. Despite these safety concerns, DES use resulted in a 35% reduction in TVR and nearly 20% reduction in MACE when compared to BMS. Although attenuated, the advantage of DES use was maintained in a higher risk population and at 6 years of follow-up. Interestingly the advantage of DES over BMS observed at 1 year follow-up in patients with renal impairment was no longer present at follow-up. In such patients with rapidly progressive coronary artery disease stent type may not be as relevant (chapter 4).

First generation drug eluting stents are associated with a risk of very late stent thrombosis. Invasive coronary imaging studies and post mortem analysis of patients who succumb to this complication reveal uncovered stent struts, evidence of chronic inflammation and fibrin deposition, positive remodeling and strut malapposition. Triggered by the urgent need to address these issues, newer generation stents were developed with changes in stent platform design, development of biocompatible polymers, new drug release kinetics and strut thickness. Although stent thrombosis rates are low, the clinical manifestations are often serious, resulting in myocardial infarction and sometimes cardiac death. Studying such events therefore requires large cohorts and for this reason the Bern-Rotterdam joint registry was set-up. Comparing more than 4000 patients in

each stent type group, we were able to demonstrate that the use of newer generation everolimus eluting stents (EES) resulted in a 58% reduction in ST when compared to SES and 68% when compared to PES at 4 years. Moreover, the benefit of EES was more pronounced during the late period with a 67% and 76% reduction in very late stent thrombosis when compared to SES and PES respectively. Importantly, a lower risk of cardiac death or myocardial infarction was observed when comparing EES and PES, a direct result of the reduced risk of stent thrombosis. This constitutes an important advance in DES safety.

The current annual incidence of very late stent thrombosis is as low as of 0.2 % with the newer generation DES. The development of a fully bioabsorbable stent/scaffold may be a permanent solution for complete elimination of the risk of very late stent thrombosis. At five years after implantation of the first generation bioabsorbable everolimus eluting scaffold, invasive imaging studies clearly show a complete bioresorption of the scaffold and thereby elimination of a substrate for the late stent complication. The benefits of this new promising stent technology need to be confirmed in clinical outcome studies.

Percutaneous coronary intervention in acute coronary syndromes, particularly ST segment elevation myocardial infarction (STEMI), is considered a higher risk intervention for several reasons. The patient is more often haemodynamically unstable, the coronary lesions contain often atherothrombotic material, there is often no flow beyond the culprit lesion and importantly the at- risk myocardium and microvascular flow is impaired. This means that restoration of epicardial flow is, unlike most stable coronary syndromes, not enough to regain myocardial function. In a patient level data meta-analysis from studies utilizing CE MRI to measure microvascular obstruction (MO) after primary percutaneous coronary intervention (PPCI) we found that more than 50% of patients with a TIMI III flow in the epicardial artery have MO. The presence of MO is an independent predictor of MACE at 2 years. Efforts to reduce events in patients with STEMI should therefore be able to demonstrate a reduction in occurrence of MO. Post conditioning has been suggested as one of the possible therapeutic options to protect myocardium during PPCI. In a retrospective exploratory study we found that patients undergoing more than 4 culprit artery balloon inflations have a lower enzymatic infarct size which however did not result in improved clinical outcomes.

A high thrombotic burden is known to be associated with higher risk of no –reflow and thrombus reduction by aspiration has been shown to improve myocardial perfusion and possibly improve clinical outcome. We explored the effect of thrombus aspiration on intra-coronary atherothrombotic material and the impact of the latter on microvascular perfusion utilizing optical coherence tomography (OCT). Safety and feasibility of the invasive imaging technique was established. A novel method of measuring residual ath-

erothrombotic burden (ATB) by OCT was developed. Interestingly OCT allows detection of residual atherothrombotic material after stent implantation that is not appreciated by angiography. Patients with a high ATB are more likely to show impaired microvascular flow as measured by myocardial blush grade and ST segment resolution.

The SYNTAX score quantifies angiographic coronary artery disease extent, lesion complexity and takes into account the patency of the artery and the myocardial area supplied by the vessel at the level of the lesion. In this thesis, (chapter 5), the value of the score in the STEMI population is assessed. A STEMI database constructed from clinical data and angiographic analysis of consecutive patients treated for acute STEMI at the Thoraxcenter, EMC in Rotterdam was used. The score performed before or after wiring of the infarct related artery has been shown to be an independent predictor of mortality and MACE at 1.5 years. It provides additional prognostic information when added to established clinical risk scores, particularly the TIMI risk score. The score has also been found to be an independent predictor of myocardial no-reflow with a score of >21 associated with a double risk. Identification of such patients at risk in the diagnostic phase of primary PCI may instigate strategies to prevent the occurrence of this important complication. The MI SYNTAX score was further validated in a contemporary multicenter STEMI trial, the COMFORTABLE AMI trial. In this stent trial (biolimus-eluting stent versus bare-metal stent), differences in clinical outcome between the stent types were most evident in the highest MI SYNTAX score groups.

The SYNTAX score was also applied to the patients with CABG in the CABG SXscore, using the SYNTAX –LE MANS substudy. At 5 year follow-up all cause death was higher in the highest score (>22) compared to low. Secondary revascularization with PCI in grafts is superior with drug-eluting stents as compared to bare-metal stents. In the Bern Rotterdam cohort we found no difference between drug eluting stent type in treatment of grafts.

In the last chapter of the thesis the application of a novel dedicated bifurcation stent device is explored. The tryton stent has been developed to facilitate the culotte technique. The stent that is placed in the proximally in the main branch and distally in the sidebranch and is designed to allow easy recross through the struts for placement of a main horse stent in the main vessel across the bifurcation. Angiographic success rates were remarkable and six month MACE and TVR rates were encouraging. The application of the dedicated stent in the left main stem also showed good angiographic results. The expected higher TVR rates warrant further intravascular imaging analysis for further improvement of the technology.

SAMENVATTING

De ontwikkeling van drug eluting stents (DES) heeft geleid tot een belangrijke en significante verbetering van de effectiviteit van de percutane behandeling van kransslagaderlijden. (hoofdstuk 1) De remming van in-stent neo-intima hyperplasie resulteerde in een enorme afname van de noodzaak tot herhaalde revascularisaties na een jaar. Dit is duidelijk aangetoond door middel van de landmark trials en de registries die de eerste generatie sirolimus eluting stents (SES) en paclitaxel eluting stents (PES) vergeleken met bare metal stents (BMS). Lange termijn follow up data toonden een cumulatieve toename aan in de incidentie van target vessel revascularisatie (TVR) bij patiënten die behandeld werden met DES leidend tot de vrees voor een mogelijk catch-up fenomeen. Met de data van RESEARCH (Rapamycin eluting stent evaluated at Rotterdam Cardiology Hospital) en T SEARCH (Taxus Stent evaluated at Rotterdam Cardiology Hospital) kon het blijvende voordeel van SES en PES ten opzichte van BMS worden aangetoond gedurende een follow up duur van 4 jaar bij patiënten met stabiel kransslagaderlijden (hoofdstuk 2)

Gedurende deze follow up periode bleek dat het gebruik van SES en PES een afname van 50% liet zien in TVR procedures alsmede een 34% afname van major adverse cardiac event rates (MACE) in vergelijking met het gebruik van BMS. De aanvankelijk gevonden trend tot een hogere incidentie van late stent trombose bij gebruik van DES bij een follow up van 4 jaar bleek statistisch significant, met meer events in de grotere 'all-comer' studie bij een langere follow up van 6 jaar (hoofdstuk 3)

Van belang is dat ongeveer de helft van de patiënten in dit studie cohort werden behandeld vanwege een onstabiel coronair syndroom en 20% vanwege een acuut myocardinfarct.

Ondanks deze 'safety issues' leidde het gebruik van DES tot een 35% reductie in TVR en een bijna 20% reductie in MACE in vergelijking met BMS. Het voordeel van DES werd gehandhaafd in een hoog risico populatie gedurende een follow up duur van 6 jaar. Opvallend was dat het voordeel van DES ten opzichte van BMS na 1 jaar bij patiënten met nierfunctiestoornissen niet gezien werd gedurende langere follow up duur. Bij dergelijke patiënten met snel progressief coronairlijden is het type stent wellicht minder relevant. (hoofdstuk 4).

Eerste generatie drug eluting stents worden geassocieerd met het risico op late stent trombose. Invasief coronair onderzoek en postmortaal onderzoek van patiënten die overleden aan late stent trombose toonden aan dat er sprake was van uncovered stent struts, aanwezigheid van chronische inflammatie, fibrine depositie, positieve remodeling en strut malappositie. Om deze problemen het hoofd te bieden werden nieuwe

generaties stents ontwikkeld met veranderingen in het stent platform design, ontwikkeling van biocompatibele polymeren, nieuwe drug releasing kinetiek en strut dikte.

Hoewel het risico op stent trombose laag is, blijft het een ernstige klinische complicatie; soms leidend tot een myocard infarct of overlijden. Het bestuderen van dergelijke events vereist dan ook grote patiënten cohorten en om die reden werd de gezamenlijke Bern-Rotterdam registry opgezet. Door middel van de analyse van PCI gegevens meer dan 4000 patiënten kon worden aangetoond dat het gebruik van nieuwe generatie everolimus eluting stents (EES) leidde tot een 58% reductie in ST ten opzichte van SES en een reductie van 68% ten opzichte van PES gedurende 4 jaar follow-up. Daarbij werd ook gezien dat het voordeel van EES duidelijker was in de latere fase met een 67% en 76 % reductie van later stent trombose wanneer vergeleken met SES en PES achtereenvolgens.

Van belang is dat een afname van het risico op cardiaal overlijden of myocard infarct werd gezien bij vergelijken EES en PES; een direct gevolg van de afname van het risico op stent trombose. Dit is een belangrijke ontwikkeling in de veiligheid van DES

De huidige jaarlijkse incidentie van late stent trombose bij het gebruik van nieuwe generatie DES is om en nabij 0.2%

Mogelijk dat de ontwikkeling van volledige bioabsorbable stents/scaffold de oplossing is voor het doen verdwijnen van het risico op late stent trombose. Door middel van imaging studies is aangetoond dat vijf jaar na implantatie van de eerste generatie bioabsorbable everolimus eluting stent/scaffold er sprake is van complete resorptie van de scaffold waarbij dus het substraat voor late stent complicaties verdwenen is. De voordelen van deze nieuwe stent technologie dienen te worden bevestigd in klinische studies.

Percutane interventies bij acute coronair syndromen, in het bijzonder bij het ST elevatie myocard infarct (STEMI) is een hoog risico ingreep vanwege meerdere redenen: hemodynamisch instabiele patiënt, de laesie bevat vaak atherotrombotisch materiaal, er is vaak geen flow na de culprit laesie en de flow naar het bedreigde myocard is op microvasculair niveau kritisch. Dit betekent dat, in tegenstelling tot stabiele coronair syndromen, het herstel van epicardiale flow onvoldoende is om de myocardiale functie te herstellen.

Door een meta analyse van MRI studies waarbij microvasculair obstructie (MO) werd gemeten na primaire percutane coronair interventie (PPCI) kon worden aangetoond dat bij meer dan 50% van patiënten met TIMI III flow in de epicardiale coronair arterie, sprake is van MO. Het optreden van MO is daarbij een onafhankelijke voorspeller van MACE bij follow up duur van 2 jaar.

Pogingen om de complicaties te reduceren bij patiënten met STEMI zullen moeten focussen op een afname van het optreden van MO. Een van de mogelijke therapeutische opties zou post conditioning kunnen zijn om het myocard te beschermen in geval van PPCI. Wij toonden aan in een retrospectieve studie dat patiënten die meer dan 4 'culprit vessel' ballon inflaties kregen, enzymatisch een kleiner infarct hadden hetgeen overigens niet resulteerde in een verbetering van de klinische uitkomstmaten.

Het is bekend dat een hoge mate van atherotrombose geassocieerd is met een verhoogd risico op no-reflow en dat de reductie van de trombogene massa door middel van aspiratie leidt tot verbeterde myocardiale perfusie met mogelijk verbetering van de klinische uitkomstmaten.

Wij onderzochten de effecten van trombosuctie op intracoronair atherotrombotisch materiaal en de impact daarvan op microvasculaire perfusie door gebruik te maken van optical coherence tomography (OCT).

De veiligheid en toepasbaarheid van deze invasieve beeldvormende techniek werd onderzocht.

Een nieuwe methode om 'atherotrombotic burden' (ATB) met behulp van OCT te meten werd ontwikkeld.

Opvallend is dat het door middel van OCT mogelijk is om rest-atherotrombotisch materiaal aan te tonen hetgeen niet gezien wordt bij angiografie. Patiënten met hoge ATB hebben vaak verminderde microvasculaire flow zoals wordt aangetoond met de graad van myocardiale blush en resolutie van het ST segment.

Door middel van de SYNTAX score kan de uitgebreidheid van coronairlijden angiografisch worden gekwantificeerd door bepalen van de patency van de kransslagader en de grootte van het bedreigde gebied. In dit proefschrift (hoofdstuk 5) wordt de bijdrage van de SYNTAX score bij STEMI beschreven. Er werd gebruik gemaakt van een STEMI database met klinische en angiografische data van STEMI patiënten behandeld in het Thoraxcentrum, EMC te Rotterdam.

De score (bepaald voor- of na 'wiring' van de infarct gerelateerde arterie) blijkt een onafhankelijke voorspeller te zijn van mortaliteit en MACE na 1.5 jaar follow up. De score voegt aanvullende prognostische informatie toe aan de bekende klinische risico scores zoals bijvoorbeeld de TIMI risk score. Ook bleek de SYNTAX score een onafhankelijke voorspeller te zijn van myocardiale no-reflow waarbij een score van meer dan 21 geassocieerd was met een verdubbeling van het risico.

De identificatie van hoog risico patiënten in de diagnostische fase voor de primaire PCI kan leiden tot een behandeling om ernstige complicaties te voorkomen.

De MI SYNTAX score werd geëvalueerd in een actuele multicenter

STEMI trial, de COMFORTABLE AMI trial. Het bleek dat in deze stent trial (biolimus-eluting stent versus bare-metal stent), de verschillen in klinische uitkomstmaten tussen de stent typen het grootst waren in de groepen met de hoogste MI SYNTAX scores.

De SYNTAX score werd ook toegepast bij CABG patiënten in de CABG SXscore,

Bij de SYNTAX –LE MANSsubstudy. Na een follow up van 5 jaar bleek de totale mortaliteit hoger te zijn in de groep met de hoogste score (>22) ten opzichte van de lage score. PCI van bypass grafts geeft betere resultaten met drug eluting stents dan met bare metal stents. Wij konden in de Bern-Rotterdam studie geen verschil aantonen tussen het gebruik van verschillende drug eluting stents bij de PCI behandeling van grafts.

Het laatste hoofdstuk beschrijft de resultaten van het gebruik van een nieuwe bifurcatie stent. De Triton stent is ontwikkeld ter verbetering van de culotte techniek. De stent wordt proximaal gepositioneerd in de hoofdtak en distaal in de zijtak en is dusdanig gevormd dat makkelijke passage door de struts mogelijk is voor plaatsen van een DES stent in de 'main branch'.

De angiografische resultaten zijn opvallend goed en MACE na 6 maanden follow up evenals TVR zijn hoopgevend. Het gebruik van de stent in de linker hoofdstam leidde eveneens tot goede angiografische resultaten.

De mogelijk hogere TVR percentages maken verder intravasculair imaging onderzoeken noodzakelijk om de techniek verder te verbeteren.

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BOOK CHAPTERS

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