NIFEDIPINE AND METOPROLOL IN SUSPECTED UNSTABLE ANGINA

The Holland Interuniversity Nifedipine/metoprolol Trial

(HINT)

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NIFEDIPINE EN METOPROLOL BIJ PATIENTEN DIE VERMOEDELIJK EEN EPISODE VAN ONSTABIELE ANGINA PECTORIS DOORMAKEN

Holland Interuniversity Nifedipine/metoprolol Trial (HINT)

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de
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en volgens besluit van het College van Dekanen.

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Introduction

THE HINT RESEARCH GROUP

It is now well accepted that the role of newly developed drugs used in the clinical management of patients needs to be evaluated in properly designed randomised clinical trials. In 1980, the Interuniversity Cardiology Institute of the Netherlands initiated the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). The objective of this randomised, double-blind, multicentre trial was to evaluate the effectiveness of nifedipine (a calcium antagonist) and metoprolol (a beta blocker) in preventing recurrence of ischaemia or progression to myocardial infarction in patients suspected of having unstable angina at hospital admission, a topic which at that time had not been well investigated. The trial was designed to follow cardiologic practice as closely as possible. In particular, patients were entered as soon as unstable angina was suspected at hospital admission, without waiting for enzyme assessments to exclude evolving myocardial infarction.

The first patient was enrolled on 1 February 1981. On 30 October 1984 patient enrolment was discontinued because an interim analysis suggested that the risk of myocardial infarction was higher in patients assigned to nifedipine than in patients treated with the other trial medications. The main findings have been published previously[1]. This supplement of the *European Heart Journal* provides a more detailed report.

In chapter 1 the pathophysiology of unstable angina pectoris is delineated. Special attention is given to new insights developed since 1980. An overview of anti-anginal drugs is provided. In addition, strategies and concepts in patient management in unstable angina are sketched. Principles of intervention research are outlined in chapter 2. It is stressed that the objective of a clinical trial is to obtain a valid and precise estimate of the magnitude of the treatment effect(s) at issue. The requirements for validity of methodology are formulated. Furthermore, the concept of scientific generalization is touched upon. In chapter 3 eligibility and patient enrolment in HINT are described. A profile of 537 randomised patients who satisfied the eligibility criteria in terms of descriptive baseline characteristics is given. In chapter 4 the trial regimens and methods of data collection are described. The occurrence of recurrent ischaemia or myocardial infarction within the first 48 hours is documented for each trial medication group separately. In addition, findings of subsequent angiography are presented. Chapter 5 is concerned with data analysis. A short introduction to data analysis is provided. The need to use risk summarization in the assessment of baseline comparability is stressed. Stratified analysis is employed to obtain estimates of the treatment effects that have been adjusted for incomparability in baseline risk. Subgroup analyses to identify subgroups of patients in whom different treatment effects may be operating are described. The study organization is the subject of chapter 6. The various committees and their responsibilities and functioning are described, as is the organization within the Clinical Centres and the Coordinating Centre. Special attention is paid to data management and quality control. Chapter 7 documents monitoring of the ongoing trial. Full details on the interim reports on treatment effects are provided. In chapter 8 recent evidence from clinical trials in the treatment of patients with prolonged anginal pain at rest is reviewed. A general discussion of the HINT findings in the light of practice today is provided in chapter 9.

Reference

[1] Early treatment of unstable angina in the coronary care unit: a randomised, double-blind placebo-controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both. The HINT Research Group. Br Heart J 1986; 56: 400–13.

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1 Unstable angina pectoris

J. G. P. TIJSSEN, M. L. SIMOONS, P. J. DE FEIJTER, P. G. HUGENHOLTZ AND J. LUBSEN

Angina pectoris

The term angina pectoris was first used by William Heberden, who described the characteristics of the syndrome in a report published in 1772[1]. He wrote:

> There is a disorder of the breast, marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, of which I do not recollect any mention among medical authors. The seat of it and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris.
>
> Those who are afflicted with it, are seized while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away if it were to increase or to continue: the moment they stand still, all this uneasiness vanishes. In all other respects the patients who are at the beginning of this disorder are perfectly well, and in particular have no shortness of breath, from which it is totally different.

As described by Heberden, angina pectoris was a symptom complex; there was no implied association with the heart[2]. It was C. H. Parry[3] who first proposed in 1799 that the pain was due to the heart being provided with a blood supply less than it required, particularly on exercise[4]. Today, the term is still used to describe a symptom, but one which is thought to be the consequence of myocardial ischaemia[2]. A transient and reversible inadequacy of the coronary circulation gives rise to that type of chest pain known as angina pectoris[2]. The stimulus to the pain is thought to originate from the myocardium becoming ischemic. If the reduction in coronary blood flow is so severe as to cause death of an area of the myocardium, the pain is usually more severe and prolonged [2].

Anginal pain has four major attributes: its character, its location, its relation to exercise, and its duration[2]. Anginal pain usually conveys a sense of strangling; other adjectives include 'constricting', 'burning', 'sharp'. Many patients deny actual pain but refer only to a sense of discomfort or tightness of the chest. The site of the pain is usually retrosternal but radiation is common, in particular to the left arm. Angina pectoris is usually provoked by exertion but may also be induced by emotion, anger, or cold environment. Most attacks are short-lived, dissipating after cessation of the precipitating activity.

In most patients, angina pectoris can be identified by analyzing the symptoms related by the patient. The fact that the pain of angina is not uniform and that other entities can mimic it makes the differentiation of other disorders from angina pectoris at times difficult. It is well known that certain emotional, gastrointestinal, pulmonary, and noncoronary cardiovascular conditions may also produce chest pains that resembles angina. In most of these disorders angina pectoris can be excluded by a careful history and physical examination. Yet, considerable skill on the part of the physician is required to identify the particular variety of chest pain that is caused by myocardial ischaemia.

Angina pectoris as described above may be considered a causally defined disease entity—for the defining criterion hinges on myocardial ischaemia as the cause of the chest pain. From the practical point of view, however, angina pectoris must be considered a clinical syndrome, the diagnosis of which is based on the presence of a variety of clinical symptoms. In fact, no well-defined series of nosographic characteristics defining angina pectoris is available. Thus, the diagnostic reasoning in establishing angina pectoris contains interrelated elements of pattern recognition, causal reasoning, and probabilistic thinking.

Attacks of angina pectoris are commonly provoked by effort or emotional stress. But angina pectoris may also occur at rest without an apparent precipitating cause. Angina pectoris (of effort) is said to be stable when there has been no change in the frequency, duration, or precipitating factors during the preceding 60 days[5]. All other presentations of angina pectoris are subsumed under the heading 'unstable angina'.

The most frequently recognised underlying cause of myocardial ischaemia (and thereby of angina pectoris) is obstructive coronary atherosclerosis. But it may also be caused by nonatherosclerotic cardiac disease such as severe aortic valve disease, hypertension, or even congenital disorders. Furthermore, vasoconstriction of the larger coronary vessels, whether or not superimposed on an atherosclerotic

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plaque, may also cause myocardial ischaemia. Finally, a decrease in arterial oxygen content, which can result from anaemia or pulmonary dysfunction, may precipitate myocardial ischaemia.

The remainder of this chapter is concerned with atherosclerotic coronary heart disease—that is, coronary atherosclerosis and its clinical manifestations.

Pathophysiology of atherosclerotic coronary heart disease

PATHOLOGY OF CORONARY ATHEROSCLEROSIS

Coronary atherosclerosis is a pathological condition of the coronary arteries characterised by abnormal lipid and fibrous tissue accumulation in the vessel wall with resulting disruption of the vessel architecture and function[5]. These atheromatous lesions or atherosclerotic plaques have a necrotic centre of fatty debris—the atheroma—covered by a fibrous cap. The density and thickness of the overlying cap may vary considerably. These focal plaques may become thick and encroach upon the lumen of the coronary artery. In addition, the fibrous cap may rupture, which may lead to ulceration of the necrotic core, platelet aggregation, and fibrin deposition (thrombus formation). The thrombus itself is biologically unstable. Lysis, fragmentation, progression to an occlusive thrombus, or incorporation lie ahead[6–9]. Plaque rupture may also cause vasoconstriction either mechanically or chemically via vasoconstrictive substances released from aggregated platelets at the rupture site[6,10].

There are currently at least two schools of thought regarding the initiating factors in the formation of coronary atherosclerosis[11]. The first believes in the endothelial injury theory where a minor lesion on the endothelial surface leads to adherence of platelets and subsequently to smooth muscle cell proliferation[12]. In this concept the platelets play a primary role in the initiation of the atherosclerotic process. The other school of thought believes that atherosclerosis and thrombosis are, initially at least, separate disorders and that the initiating factor in atherosclerosis is the deposition of excess lipids in the vessel wall[13]. As the lesion grows into the atherosclerotic plaque, a rupture in the latter can lead to haemorrhage which in turn provokes rapid aggregation of platelets and thrombosis[6,14]. In both concepts it is believed that the smooth muscle cell is at the heart of the reactive connective tissue proliferation in the subintimal cells of the media[15]. As Becker pointed out recently, no unifying theory can at present be offered, but it is clear that the 'classical' atherosclerotic lesion or plaque remains a major end point[15].

While aetiology of coronary atherosclerosis remains to be clarified, but a number of predisposing factors have been identified: a family history, hyperlipidaemia, hypertension, smoking of cigarettes, diabetes mellitus, and obesity.

CORONARY BLOOD FLOW AND MYOCARDIAL ISCHAEMIA

The coronary circulation is capable of autoregulation—flow increases with augmented oxygen demand and falls with reduced demand. This adjustment is achieved by means of appropriate alterations in coronary vascular resistance. The major determinants of myocardial oxygen demand are heart rate, wall stress, and contractility. Wall stress of the left ventricle is determined by left ventricular systolic pressure, left ventricular end-diastolic volume, and wall thickness. The determinants of oxygen supply are heart rate, aortic diastolic pressure, left ventricular end-diastolic pressure, and coronary vascular resistance (tonus and diameter). In addition, oxygen supply depends on haemoglobin concentration and on arterial oxygen saturation, which is determined by lung function.

Coronary atherosclerosis may lead to a progressive narrowing of the coronary lumen to the degree that blood flow to the myocardium is impeded. In addition, thrombotic processes which occur at the site of a ruptured plaque may further reduce or even obstruct coronary blood flow. Myocardial ischaemia occurs when coronary blood flow is unable to meet the myocardial demand for oxygen and nutrients. The consequences of myocardial ischaemia include, besides anginal pain, metabolic and electrophysiological changes, cessation of local myocardial contraction, and sometimes ventricular failure. Myocardial ischaemia initially causes metabolic changes in the affected cells characteristic of reversible injury: restoration of arterial flow and oxygenation prevents cell death and allows the affected cells to begin functioning again. Prolonged or severe myocardial ischaemia causes irreversible injury to the affected cells: the cells die and cannot be salvaged by re-oxygenation. The term myocardial infarction is therefore used to indicate necrosis of a portion of heart muscle as a result of inadequate blood supply[2]. The occlusion of a coronary artery by thrombus (i.e. coronary thrombosis) usually causes myocardial infarction, although prolonged mild ischaemia may also cause myocardial infarction.

CLINICAL MANIFESTATIONS

Coronary atherosclerosis may lead to a variety of syndromes which can affect the same patient at different times. These are stable angina pectoris, unstable angina pectoris, acute myocardial infarction, cardiac failure, arrhythmia, and sudden death (not necessarily in that sequence)[2].

Patients may have coronary atherosclerosis which is not sufficiently severe to impede coronary blood flow. Such patients usually have no symptoms. Also, in more gradually developing atherosclerosis collateral flow may become so extensive that major symptoms do not develop. However, if coronary atherosclerosis has progressed to a degree that coronary flow reserve is critically limited, myocardial ischaemia (and angina as its clinical counterpart) consistently develops when a sudden increase in myocardial oxygen demand exceeds the capacity of the coronary artery to supply blood. Removal of factors causing increased myocardial oxygen demand (exercise or emotional stress) eliminates myocardial ischaemia within minutes and prevents irreversible injury to the heart muscle. The absence of anginal complaints or the presence of stable, exercise induced angina characterise the clinically stable phase of atherosclerotic coronary disease.

Sudden critical changes in the degree of flow obstruction originating from the atherosclerotic lesion may precipitate acute syndromes interrupting the phase of clinical stability. Changes in flow obstruction that only affect coronary flow reserve manifest themselves in changes in the level of exertion at which angina occurs (the anginal threshold). If the change in flow obstruction prohibits further support of the resting metabolism of the myocardium, myocardial ischaemia and chest pain, either of the anginal type or typical for myocardial infarction, will occur without being provoked by exertion. Also, myocardial ischaemia may occur without causing a sensation of chest pain—this phenomenon is referred to as silent ischaemia.

Plaque rupture or endothelial ulceration followed by platelet aggregation or a thrombotic process are generally considered pivotal factors in sudden changes in the degree of flow obstruction and hence in the conversion from clinical stability to clinical instability[6–9]. The formation of a partial occlusive thrombus on the site of a ruptured plaque could be the basis for a sudden decrease of myocardial oxygen supply with angina at rest or a dramatic decrease in anginal threshold as its clinical counterpart[16–19]. As stated before, the degree of flow obstruction and its duration (together with the amount of collateral flow) determine the extent of irreversible injury (necrosis) induced in the myocardium at risk. Timely lysis of a partially occlusive thrombus would imply a return to stability without myocardial infarction. Occlusive thrombus formation (not followed by timely lysis) or prolonged severe partial occlusion will lead to acute myocardial infarction[20,21]. Incorporation of a partial occlusive thrombus in the plaque could lead to further but slower progression of coronary atherosclerosis with stable angina at a lower threshold as its clinical manifestation[9]. Recurrent episodes of thrombus formation and thrombus disintegration could be the basis of recurrent episodes of angina or of ischaemic myopathy[6]. Fragmentation of the thrombus can lead to sudden death[6]. Finally, vasoconstrictive phenomena, either through platelet activation or otherwise, also play a role in the precipitation of clinical instability[19,22].

Newly developed angioscopes have allowed direct *in vivo* examination of the endothelial surface of the coronary artery during unstable coronary syndromes. Sherman and co-workers observed ragged, ulcerated, haemorrhagic endothelium and acute thrombi in the pain related coronary artery in patients with unstable angina who underwent coronary surgery because pharmacologic management had failed[23]. Comparable endothelial lesions were not seen in patients with stable syndromes. These observations suggest that instability of the plaque makes some atherosclerotic lesions more susceptible to thrombosis and vasoconstriction than others. The severity of the fixed atherosclerotic lesion seems to be a major determinant for the ultimate outcome of the thrombotic process. Progression to an occlusive thrombus or plain spasm (i.e. abnormal vasoconstriction leading to complete occlusion) could occur more easily when the vascular lumen is already critically reduced by severe atherosclerosis, especially if the remaining lumen is eccentric[24].

Methods used to identify acute clinical syndromes due to atherosclerotic coronary heart disease

The physician utilizes the patient's history, the reaction to treatment, the physical examination, and certain laboratory techniques to identify acute clinical syndromes due to atherosclerotic coronary disease. Each of the diagnostic tools has value but each method has its own imperfections[5].

It is a physician's skill to elicit and to interpret a patient's history accurately. On the other hand, history as a diagnostic method has its limitations. Take as an example patients who deny symptoms

because they cannot cope with the consequences or patients who exaggerate symptoms for self gain.

The physical examination may be helpful in diagnosing acute myocardial infarction (signs of acute heart failure, vegetative symptoms, severe perspiration). It may also play a role in identifying a non-coronary cause for the chest pain. On the other hand, it must be emphasized that the patient with angina pectoris usually exhibits no abnormalities on physical examination[5].

The information gained from the electrocardiogram is valuable if serial electrocardiograms recorded during and after chest pain are available. The value of the resting electrocardiogram by itself is limited if no electrocardiograms recorded during chest pain are available. ST-segment displacements or T-wave inversions occurring during chest pain are characteristic of myocardial ischaemia. Transient abnormalities usually point towards reversible ischaemia, persisting severe ST-segment displacements towards irreversible ischaemia. On the other hand, prolonged myocardial ischaemia may occur without electrocardiographic changes. Changes in the QRS-complex characteristic of myocardial infarction usually appear within 48 hours of onset of myocardial infarction. However, these characteristic changes can be absent, particularly in small infarctions.

The technique of measuring the activities of cardiac enzymes in the blood is used to diagnose myocardial infarction. Cardiac enzymes are released from irreversibly injured myocardial cells into the circulation during a period of several hours or possibly days after onset of myocardial infarction. It takes a few hours before the enzymes appear in the circulation in sufficient amounts to become detectable after ischaemia has brought irreversible damage on the myocardium[25]. As no instantaneous techniques for the determination of enzyme levels are routinely available, an additional laboratory delay is unavoidable. As a result, enzymatic confirmation of myocardial infarction usually becomes available not until eight hours or more after its onset. Therefore, enzymatic detection of myocardial infarction plays a key role in the retrospective assessment of episodes of clinical instability, but enzyme values are of little importance in the early differentiation between reversible and irreversible ischaemia.

The syndrome of unstable angina pectoris

Unstable angina as defined above comprises all clinically unstable manifestations of coronary atherosclerosis in which myocardial ischaemia causes only reversible injury to the myocardium. Other terms such as impending myocardial infarction, threatened myocardial infarction, acute coronary insufficiency, or the intermediate coronary syndrome have been used in this context. Unstable angina has become the currently preferred term, connoting the instability of the clinical situation[26].

The syndrome of unstable angina encompasses a wide variety of distinct clinical presentations. Three different categories are usually distinguished: (1) angina of effort of recent onset; (2) angina of effort with a changing pattern, usually progressive; (3) angina at rest[27]. Within the category of angina at rest several subcategories can be identified, such as variant angina, refractory angina, postinfarction angina. The term variant angina, originally proposed by Prinzmetal, is used to describe angina at rest associated with transient ST-segment elevation in the electrocardiogram in patients with normal exercise tolerance[28]. Patients in whom attacks of angina at rest repeatedly occur in spite of (vigorous) pharmacologic treatment are referred to as having refractory angina[29]. The term postinfarction angina is adopted when patients develop unstable angina during the recovery phase after myocardial infarction. Each of the above (sub)categories may be viewed as a separate syndrome.

Angina at rest may appear de novo or may occur in a patient with stable or progressive angina of effort. There may be single or there may be multiple episodes, lasting from minutes to one hour. ST-segment depression or ST-segment elevation may be observed in the electrocardiogram during an attack. In addition, it may produce T-wave inversions in the electrocardiogram that require hours or even days to return to normal. Notwithstanding Conti's definition, the term 'unstable angina' is also often used to refer to episodes of prolonged (more than 15 minutes) anginal pain at rest, with accompanying ST-segment or T-wave changes in the electrocardiogram[26,30]. Some authors still refer to this specific condition as the 'intermediate coronary syndrome'[31]. It forms a subcategory of Conti's third category and may also include Prinzmetal's syndrome[27,28].

Current anti-anginal drugs

In the treatment of angina pectoris a distinction must be made between the treatment to eliminate acute chest pain and maintenance treatment to prevent episodes of angina pectoris or to diminish their frequency.

Treatment of acute chest pain starts with limitation

Table 1.1 Influence of oral nitrates, oral beta blockers, and oral calcium antagonists on myocardial oxygen consumption and oxygen supply

	Decrease oxygen consumption				Increase oxygen supply	
	Decrease heart rate	Decrease syst blood pressure	Decrease LV end-diast vol	Decrease Contractility	Decrease coronary resistance	Increase diast blood pressure
Nitrates	−	+	+	0	+	−
Beta blockers	+	+	−	+	0	−
Nifedipine	−	+	0	0	+	−
Verapamil	+	+	−	+	+	−
Diltiazem	+	+	−	+	+	−

syst, systolic; LV, left-ventricular; diast, diastolic, vol, volume;
+, a salutary effect on the oxygen balance;
0, no effect on the oxygen balance;
−, a detrimental effect on the oxygen balance.

of those factors and conditions which initiated the attack, aided in some patients by sedation. If chest pain persists, it can be relieved by the sublingual use of nitrates (glyceryl trinitrate or isosorbide dinitrate) or by a capsule of nifedipine. Opiates are usually needed to relieve the pain associated with more severe ischaemia, suspected to be of acute myocardial infarction.

Episodes of anginal pain may also be prevented by readjustment of the factors determining oxygen consumption and oxygen supply. Nitrates, beta blockers, and calcium antagonists, either alone or in combination, are advocated as being useful in this context. Their influences on oxygen consumption and oxygen supply of the heart muscle are summarized in Table 1.1.

Nitrates increase the venous capacitance, causing pooling of blood in the peripheral veins. Myocardial oxygen demand is attenuated by the ensuing reduction in left ventricular end diastolic volume (preload) and systemic blood pressure (afterload)[32]. Nitrates may also diminish coronary vasomotor tone, which improves coronary perfusion and increases oxygen supply[33]. The most important side effects are headaches and orthostatic hypotension, but palpitations, reflextachycardia and nausea may also occur. Sublingual glyceryl trinitrate is rapidly absorbed from the sublingual mucosa. Its onset of action occurs within minutes, with maximal effects at three to 15 minutes, while little residual activity remains at 20 to 30 minutes[33]. Patients with stable angina may use the drug prophylactically prior to an activity that is known to precipitate angina pectoris. Glyceryl trinitrate in ointments and in transdermal therapeutic systems (plasters) for topical applications may be an important addition to the available anti-anginal agents for some patients[34]. Intravenous glyceryl trinitrate is now being used in coronary care units to eliminate recurrent episodes of ischaemia. Long-lasting anti-anginal effects may also be obtained from oral slow release preparations of nitrate esters, such as isosorbide dinitrate. High oral doses have to be given to overcome the rather extensive first pass liver metabolism[33]. Isosorbide mononitrate, a metabolite of isosorbide dinitrate, is characterised by more favorable pharmacokinetic properties[35,36]. However, continuous long-term use of nitrates, in particular of glyceryl trinitrate, may cause tolerance, which offsets anti-anginal effects in certain patients[37].

Beta blocking agents antagonise the actions of catecholamines on the beta receptors by competitive inhibition. Beta blockade reduces the oxygen demand by reducing heart rate and blood pressure and depressing contractility[32]. To be effective a resting heart rate of 55–60 beats min^{-1} must be achieved[32]. Beta blockers are contra-indicated in patients with signs of cardiac failure, obstructive lung dysfunction, bradycardia, or conduction disorders. Cardioselective beta blockers carry a smaller risk for bronchoconstriction than nonselective beta blockers. A systematic comparison of the efficacy of the numerous beta

blockers currently available in the management (unstable) angina has not been performed[38]. Beta blockade may cause cardiac failure. Side effects of beta blockers include cold distal limbs, impotence, and occasionally intermittent claudication, gastrointestinal dysfunction, hallucinations, coronary artery spasm, and Raynaud's syndrome.

Calcium antagonists represent a heterogeneous group of vasodilating drugs which share the ability to inhibit the transmembrane influx of calcium in all types of muscle cells. The most popular calcium antagonists are nifedipine, verapamil, and diltiazem. Although the three drugs share the same principle, they vary in their potency to affect the different components of the cardiovascular system[39]. The calcium antagonists have a direct action on the smooth muscle of certain arteries, depending on the specific compound. They inhibit or relieve coronary spasm and produce dilation of coronary arteries including both large and small arteries as well as collateral vessels, thereby causing an increased cardiac blood supply[40,41]. Furthermore, dilation of the peripheral arteriolar bed reduces vascular resistance and systemic blood pressure and thus the afterload to the heart[41]. Calcium antagonists may also decrease contractility[42]. In contrast to nifedipine, which may cause an increase in heart rate, verapamil and diltiazem usually lead to a reduction in heart rate[43]. When considered at a cellular level, it can be argued that all calcium antagonists will confer protection to the myocardium against the deleterious effect of ischaemia by slowing excessive calcium influx, by blocking early catecholamine release, by avoidance of high-energy phosphate break-down with suppression of attendant loss of purine derivatives[44,45]. However, it was recently stressed that cardioprotective effects of calcium antagonists were only observed in animal preparations when the drugs were given before the ischemic condition had been established, and that, as a logical consequence, similar effects may only be expected in clinical practice under similar circumstances, in particular that fewer benefits should be expected when calcium antagonists are given after onset of ischaemia[45]. Adverse effects are those of all peripheral vasodilators: flushing, headache, pretibial oedema. Aggravation of angina can occur in some patients, an effect possibly related to arterial hypotension in combination with reflex tachycardia or to coronary steal[43].

Apart from the afore mentioned main mechanisms each drug has a host of ancillary pharmacologic properties. For instance, nitroglycerine, beta blockers, and calcium antagonists are claimed to have mild anti-aggregatory effects on platelets[38,47]. It, however, appears difficult to judge the relevancy of these properties in the clinical situation.

Thrombolytic agents, platelet aggregation inhibiting drugs, and anticoagulants appear to be an alternative or additional approach to the current drug treatment of unstable angina, especially in view of recent patho-physiologic insights[9]. The first may lyse intracoronary thrombi, the second may inhibit platelet aggregation at the site of a ruptured plaque, and the third may prevent intracoronary thrombosis.

Management of patients with acute chest pain

INITIAL MANAGEMENT AND DIFFERENTIATION

> When examining a man for illness in his cordia, he has pain in his arms, in his breast, on the side of his cardia . . . it is death which approaches him.
>
> *The Ebers papyrus*, 3000 BC

One will never know whether the ancient Egyptian suffered from acute myocardial infarction or from unstable angina. One thing is certain, even to date, patients with the symptoms described above represent a problem in deciding whether a myocardial infarction has occurred or may still be averted by timely intervention[48].

Patients developing abrupt persistent chest pain without a precipitating cause usually seek help of a physician (the patient's general practitioner or a physician at the mobile coronary care unit, at the emergency room or at the coronary care unit itself). Treatment of chest pain is usually started without a diagnosis being made. The available medications include sublingual or intravenous glyceryl trinitrate, nifedipine, fentanyl, or opiates. If an acute cardiac problem is suspected, the general practitioner, if involved, usually refers the patient to hospital.

In the hospital an early (provisional) diagnosis is made after relief of chest pain, if still present. The patient's reaction to pain treatment, the interview, and electrocardiography are the diagnostic tools available to the physician. Each one is indispensible to identify myocardial ischaemia (either reversible or irreversible) as the (presumed) cause of the chest pain. Three diagnostic categories are available, each reflecting the physician's perception of the nature of the ischaemia: (1) suspected acute myocardial infarction, i.e. irreversible ischaemia; (2) suspected unstable angina, i.e. reversible ischaemia (3) probably no angina, i.e. no acute ischaemia. Each diagnostic category has its own therapeutic consequences.

Patients are identified as sustaining acute myocardial infarction (1) if severe chest pain has persisted for more than 30 minutes, in particular if opiates need be given to eliminate chest pain; (2) if vegetative symptoms or signs of overt cardiac failure have appeared; or (3) if typical electrocardiographic abnormalities persist or worsen. The task in early management is (1) to relieve pain, dyspnoea, and anxiety; (2) to provide continuous monitoring and prompt treatment of life-threatening arrhythmias, if they should occur; (3) to salvage as much of the jeopardized myocardium as possible; and (4) to treat left heart failure, if present. As myocardial infarction is usually caused by complete occlusion of a (major branch of a) coronary artery, thrombolytic treatment has become the first therapeutic option if the occlusion is thought to have occurred within the last four to six hours[49]. There is now substantial evidence that treatment with streptokinase (intravenously but especially intracoronary) may be useful[50–53]. Treatment with recombinant tissue-type plasminogen activator seems promising[54–56]. In addition, there is overwhelming evidence that early beta blockade marginally reduces early mortality in patients with uncomplicated myocardial infarction[57,58].

Patients are identified as having unstable angina (1) when chest pain did not last for more than 30 minutes and had ceased spontaneously or could rapidly be relieved by glyceryl trinitrate; and (2) if the electrocardiogram shows signs of reversible myocardial ischaemia. Further management is described below.

Patients with chest pain of the anginal type without further evidence for myocardial ischaemia or coronary atherosclerosis and patients with severe but as yet unexplained chest pain are usually kept in the hospital for further observation while therapeutic measures are deferred until symptoms reappear or until exercise testing or angiography is performed. Appropriate measures are taken if the chest pain can be attributed to a non-cardiac cause (e.g. peptic ulcer, oesophagitis, or gall stones) or to a noncoronary cardiac cause (e.g. aortic stenosis).

FURTHER MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA

After initial pain relief the aims of early treatment in patients identified as having unstable angina at hospital admission are the prevention of recurrent ischaemia or progression to myocardial infarction and the restoration of a stable clinical condition. As electrocardiography and severity of chest pain have limited sensitivity for irreversibility of myocardial injury, chest pain initially impressing as unstable angina may in fact originate from evolving myocardial infarction, which might be an important consideration in the determination of further management.

It is generally agreed upon that patients with unstable angina should be admitted to a coronary care unit to provide continuous monitoring and prompt treatment of life-threatening complications, if they should occur[59]. Bed rest, reassurance, and sedation may go a long way in reducing the determinants of myocardial oxygen demand[26]. It is now common practice to intensify and optimize pharmacologic treatment first, in an attempt to stabilize the acute ischaemic symptoms[26,30]. (The process of stabilizing the symptoms is often referred to as 'cooling off' unstable angina.) Nitrates, beta blockers, calcium antagonist may be useful in this respect by readjustment of factors determining oxygen demand and supply. As the main mechanisms are different, combination of these drugs may be advantageous. Some authors recommend to increase drug treatment stepwise, guided by symptoms and haemodynamics of the patient, for instance according to the scheme provided by Simoons (Table 1.2)[60]. Others recommend that triple treatment be the rule with intravenous nitrates used as necessary[31]. Treatment with heparin may also be beneficial. The role of early intravenous fibrinolytic treatment in this condition has not (yet) been delineated. Whether benefits outweigh the albeit small risks of severe bleeding complications (including cerebro-vascular accidents) remains to be established.

Table 1.2 Step-up approach in the treatment of unstable angina after hospital admission

In all patients:
Rest, sedation, correction of hypertension, anaemia, etc.

Additional pharmacologic treatment:

	Nitrates	Beta blockers	Calcium antagonists
1	oral	oral	—
2	sublingual	oral	oral
3	intravenous	intravenous	sublingual

Further invasive treatment:

4 Urgent coronary angiography, and depending on its interpretation angioplasty or surgery, and if necessary intra-aortic balloon pump

MANAGEMENT OF PATIENTS WITH REFRACTORY SYMPTOMS

It is generally agreed upon that refractory angina (i.e., persisting symptoms in spite of intensive pharmacologic treatment) forms an indication for urgent coronary angiography[26,30,61,62]. If the angiographic appearance suggests that a thrombus is present at the symptom related segment, thrombolysis may be attempted. If the symptom related lesion appears suitable for angioplasty or bypass grafting, that intervention is usually performed as soon as possible. If the intervention cannot be performed at short notice, the intra-aortic balloon pump can be used for temporary stabilization of patients awaiting further interventions.

The inoperable refractory patient has a grave prognosis. In addition to continuing and optimization of the medical treatment, the physician can only offer support and symptomatic relief with analgesics as needed[26].

MANAGEMENT AFTER STABILIZATION OF SYMPTOMS

A symptom free interval of 48 hours (in the absence of enzyme rises) is generally considered a token of restored clinical stability. It creates room for further diagnostic work-up and the determination of a long term treatment strategy. The initial months following hospital admission for unstable angina are a period of high risk of recurrence of symptoms, infarction, or death, in particular in patients with ST-segment depression[31]. After this period the risks are substantially reduced and become comparable to those of patients with stable angina[63].

Treatment aims in unstable angina patients after stabilization of symptoms are: (1) to prevent new episodes of unstable angina, myocardial infarction, or sudden death; (2) to alleviate symptoms of stable angina, if present: (3) to slow down progression of coronary atherosclerosis.

To begin with, patients should be encouraged to stop smoking, to attain a normal weight, and to achieve a normal blood pressure.

It is common practice to perform coronary angiography in most patients, except in elderly patients who are not candidates for surgery or in patients with an isolated episode of chest pain without recurrence. The knowledge gained from the angiogram can be helpful in selecting appropriate treatment. The majority of patients are found to have atherosclerotic coronary lesions, the severity of which determines long term prognosis. Angioplasty or bypass surgery seems indicated as a measure to improve prognosis, particularly in younger patients with advanced coronary lesions (even in the absence of severe symptoms)[2]. Exercise testing or continuous electrocardiographic monitoring may help to identify patients at high risk, in whom revascularization procedures may be indicated[64,63]. In other patients one may consider to continue and optimize pharmacologic treatment first and to offer angioplasty or bypass surgery when recurrent severe symptoms persist or develop. If normal or minimally diseased vessels are found, increased coronary vasomotor tone can be considered the cause of the unstable episode, provided that objective evidence of ischaemia has been obtained. Patients with this condition usually have a good prognosis[65,66].

Nitrates, beta blockers, and calcium antagonists are known to be efficacious in avoiding symptoms of stable angina, if they should occur[33,39,67]. Beta blockers may also be considered in the absence of these symptoms because of their established role in reducing mortality after myocardial infarction[68,69]. Todays insights in the pathophysiology of unstable angina suggest a major role for antithrombotic treatment in the prevention of long-term complications[9]. However, treatment with full-dose anticoagulation has not (yet) adequately been investigated. Beneficial effects of acetyl salicylic acid have been observed in large secondary prevention studies[70,71] when the drug was given after the acute episode.

TEMPORAL ASPECTS TO THE DIFFERENTIATION BETWEEN UNSTABLE ANGINA AND ACUTE MYOCARDIAL INFARCTION

Wulff has pointed out that a diagnosis is not an end in itself—it is a mental resting-place for prognostic considerations and therapeutic decisions[72]. Early differentiation between (suspected) acute myocardial infarction and (suspected) unstable angina may have considerable therapeutic consequences, for instance in regard to the institution of thrombolytic treatment or emergency revascularization procedures. As these measures may not be deferred until a final, definitive diagnosis is made, the treating physician must make a provisional, early diagnosis based upon the often scanty information available at presentation. This is a momentary (or instantaneous) diagnosis in the sense that it reflects the physician's opinion on what is going on in the coronary arteries and myocardium of the patient at that particular moment. Revision of the diagnosis may occur repeatedly, either because new information (enzyme values, details of the patient's history) becomes available or because the clinical course takes a turn

(e.g. the occurrence of new apparently uncontrollable chest pain).

Once the clinical condition of the patient has stabilized (after a pain free interval of 48 hours), the treating physician may look backward and evaluate the preceding episode of clinical instability, with a view towards further treatment. Usually, the episode as a whole is labelled. The most important categories are (confirmed) myocardial infarction, (confirmed) unstable angina, chest pain of known noncoronary origin, chest pain with unknown cause. It is customary to designate all episodes of chest pain at rest accompanied by electrocardiographic changes but without subsequent enzyme rises as episodes of 'unstable angina', even if the patient initially presented as acute myocardial infarction. Likewise, a patient initially diagnosed as having unstable angina is said (in retrospect) to have sustained myocardial infarction when subsequent enzyme values were found to be raised.

As a consequence, the differentiation between myocardial infarction and unstable angina has an important temporal aspect and should be approached from the point of view of early diagnoses (with a view to treatment of the acute illness) and late (retrospective) diagnoses (with a view to long-term secondary preventive treatment). The consequences of this distinction for the interpretation of findings from clinical trials are discussed in chapter 8.

Concepts underlying the design of HINT

The present trial—the Holland Interuniversity Nifedipine/metoprolol Trial (HINT)—was designed in the late seventies and initiated in 1981. At that time it was felt that the relative effects of the various pharmacologic treatments in the early phase of unstable angina had not been sufficiently studied[73]. While the restoration of a stable clinical condition within 48 hours in combination with the prevention of acute myocardial infarction was perceived as the primary goal of early pharmacologic treatment, it was unclear which compound or combinations thereof would be superior.

Pathophysiologic insights at that time were dominated by the concept of flow reduction due to fixed atherosclerotic lesions on which variable obstructions due to spasm or increased vasomotor tone were superimposed[74,75]. The idea was that all forms of unstable angina were in between two extremes: (1) classic stable angina resulting from a severe fixed atherosclerotic lesion which caused chest pain already at very slight exertion (95% obstruction, 5% spasm) and (2) severe spasm in the near absence of a fixed stenosis resulting in Prinzmetal's syndrome (95% spasm, 5% obstruction) (Fig. 1.1). Long-acting nitrates were supposed to be effective over the whole range. Beta blockers, and ultimately bypass surgery, were believed to be most effective if a fixed stenosis was the dominating factor. Calcium antagonists were supposed to be most effective if spasm or increased vasomotor tone was the dominating factor. Therefore, in the presence of a mixture of increased coronary vasomotor tone and a fixed lesion a combination of a beta blocker and a calcium antagonist might be useful. It followed from this that the therapeutic choice between a beta blocker and a calcium antagonist should depend on the treating physician's perception of the underlying pathophysiology. As it was virtually impossible to assess the mix between spasm and fixed lesions in the individual patient (especially without angiography), a growing tendency emerged to commence treatment with triple treatment: nitrates, beta blockers, and calcium antagonists. In view of possible haemodynamic interactions and of the impossibility to judge the effects of the drugs separately, a step wise approach guided by the symptoms and haemodynamic condition of the patient was considered preferable.

In view of the above considerations, it was decided that the effect of a beta blocker and a calcium antagonist, either alone or in combination, in the early treatment of suspected unstable angina deserved investigation in a large scale randomised clinical trial. Long-acting nitrates were left out from the trial comparison. They would be available as back-up treatment in case of persisting symptoms. As many clinicians then believed (and still do today) that emotional and physical rest is most essential in the treatment of unstable angina, a comparison with placebo was considered justified. Of the possible beta blockers metoprolol was chosen mainly because of its long action and fixed dosage scheme. Of the calcium antagonists nifedipine was chosen because of its outspoken spasmolytic effect on the coronary arteries and because of promising findings in non-randomised studies[40,76]. Another important consideration was the willingness of the manufacturers of these drugs to sponsor the trial in part.

Patients who develop unstable angina while already on maintenance treatment with a beta blocker, must be considered a failure of beta blocker treatment. The addition of nifedipine to the regimen was a therapeutic option worthy of further investigation—for one might argue that among other factors enhanced vasoconstriction might be the

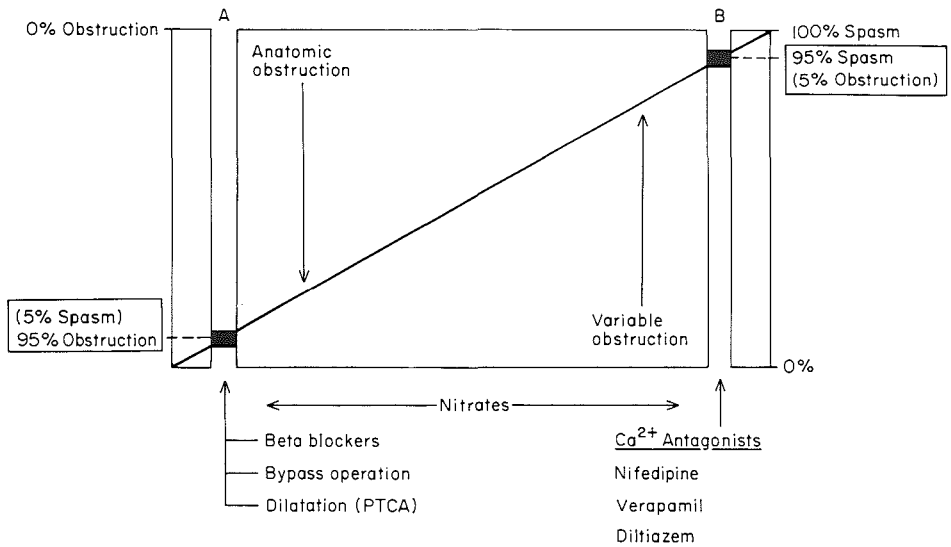

Figure 1.1 Causes of the various forms of unstable angina as they were perceived at the time when HINT was designed (1980): 'The therapeutic approach to the various forms of unstable angina depends on the clinician's awareness of the underlying pathophysiology. If a 'fixed' stenosis is suspected, the first choice of treatment will be quite different than when spasm is the most likely cause of the symptoms. Most cases will lie in between and therefore require individual assessment of the situation in order to achieve optimal choice of treatment' (PTCA—percutaneous transluminary coronary angioplasty).

dominant factor in these patients. A comparison with placebo seemed ethically justifiable by the same argument as above.

Thus, a clinical trial was designed in patients with unstable angina at hospital admission—that is, after an episode of prolonged (> 15 min) chest pain at rest due to reversible ischaemia as perceived by the treating physician after relief of chest pain. In patients not on previous maintenance treatment with a beta blocker, treatment with nifedipine, metoprolol, or the combination was compared to treatment with placebo in its capacity of restoring clinical stability within 48 hours. In patients on previous maintenance treatment with a beta blocker the effect of nifedipine was compared to that of placebo, whilst beta blockade was continued.

General outline of the trial design of HINT

Patients admitted to a coronary care unit after one or more episodes of chest pain at rest were screened for inclusion in the trial. The inclusion criteria required elimination of existing chest pain by sublingual glyceryl trinitrate and ST segment or T-wave changes on the electrocardiogram suggestive for reversible ischaemia. For patients admitted to hospital after spontaneous relief of chest pain, the inclusion criteria required either an abnormal resting electrocardiogram or other evidence of atherosclerotic heart disease. The exclusion criteria comprised signs and symptoms of acute myocardial infarction, known extracardiac cause of myocardial ischaemia, the usual contra-indications for nifedipine or beta blockers, and previous maintenance treatment with nifedipine.

All patients received usual medical care—that is, bed rest, sedation, and electrocardiographic monitoring. Patients not on previous maintenance treatment with a beta blocker were randomly assigned to receive either double placebo, nifedipine plus metoprolol placebo, metoprolol plus nifedipine placebo, or both drugs. Patients on previous maintenance treatment with a beta blocker were randomised to receive either nifedipine or placebo, whereas their beta blockade was continued. Trial medications were started as soon as possible after relief of chest pain. They were continued for at least 48 hours unless contra-indications developed.

Trial medications were compared as to percentage of patients who developed acute myocardial infarction or who experienced recurrent myocardial ischaemia within 48 hours of randomisation. Acute myocardial infarction was established if enzyme values were raised over twice the upper limit for normal. Recurrent myocardial ischaemia was

inferred from the recurrence of chest pain with ST-segment or T-wave changes. The clinical course of each patient was documented and independently reviewed by a panel of experts with a view to establish whether myocardial infarction or recurrent ischaemia had taken place.

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2 Principles of intervention research

J. G. P. Tijssen and J. Lubsen

Introduction

It was P. C. A. Louis who already in 1835 urged that future evaluations of treatment should use the 'numerical method', which had served him so well in denouncing the practice of blood letting in inflammatory disease[1]. Although the interest never completely vanished in the intervening period, the need to devise objective ways to evaluate medical interventions found renewed interest in the 1930s and 1940s. In those days the need to evaluate different treatments in groups of patients with comparable prognosis treated in different ways was clearly recognised as was the need for blind evaluation[2]. The concept of randomisation as a device for treatment allocation was introduced by Fisher to agricultural experimentation in 1923[3]. Although random treatment allocation had been applied before in clinical experiments, the 1948 Medical Research Council trial on the use of streptomycin in the treatment of pulmonary tuberculosis is generally considered as pioneering work in the development of the multicenter randomised clinical trial as treatment evaluation method[4].

From the beginning of medicine physicians have found cures that with the passage of time have proven to be useless. In contemporary medicine it has become accepted that medical interventions are critically evaluated in the clinical setting before being introduced to clinical practice. Pathophysiologic and pharmacologic insights, usually the result of basic research, engender a hypothesis (or a theory) that a certain clinical intervention may be efficacious in a certain disease. Clinical investigators subsequently design and conduct clinical studies in order to investigate clinical usefulness of the intervention. The randomised clinical trial has become the paradigm for the latter[5].

The clinical trial: a measurement device for therapeutic effects

In clinical practice it is not sufficient to just know that a certain therapeutic intervention 'works' or 'does not work'. Treatment decisions ultimately hinge on weighing the magnitude of the expected therapeutic benefit against possible adversary effects and against costs. Consequently, a clinical trial must be viewed as a device to measure treatment effect (i.e., expected therapeutic benefit) and not as a means of assessing whether a treatment effect exists or does not.

Viewing a clinical trial as a measurement device provides firm guidance in planning and carrying out a trial and in interpreting its findings as well. Consequently, the objective of a clinical trial should be stipulated in quantitative terms. As an example, the objective of a trial of beta blockers in suspected acute myocardial infarction is to 'estimate the percentage mortality reduction' rather than 'to determine whether mortality is reduced', the latter being a qualitative statement. It is noted that the above principles implies the inherent specification of a quantitative measure of treatment effect as the object of measurement.

As regards a measurement device in general, it is first and foremost necessary to identify the object of measurement. Secondly, behaviour in terms of measurement errors need be considered. For the latter, a distinction is usually made between systematic and random error.

As noted above, the object of measurement in a clinical trial is a treatment effect. As a rule, treatment effects can only be meaningfully expressed in relative terms—that is by relating disease outcome under one treatment to that under another treatment, the latter serving as reference. More specifically, a treatment effect is characterized by three elements: (1) the treatments to be compared; (2) the disease entity for which treatment effect assessment is required; and (3) the disease outcome, i.e. that aspect of the clinical course that one intends to influence.

Accuracy of a measurement device refers to lack of systematic error. A device is said to be accurate if it has the property that the value obtained by measurement equals the underlying true value on the average. The principles of clinical trial design derive from the need to avoid systematic error in measuring treatment effects. A trial that may be expected to yield accurate measurement of the treatment effect under study is said to be internally valid.

Precision of a measurement device refers to lack of random variation. An accurate measurement device is useless if the influence of random error is so

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extensive that the measured value may substantially deviate from the underlying true value. Thus, such random error must be avoided so that the value obtained by measurement can be expected to be reasonably close to the true underlying value. Precision in a clinical trial primarily depends on the size of the compared treatment groups.

In the following sections the design elements which specify the object of measurement in a clinical trial and the design features that bear on accuracy and precision are discussed in more detail.

Design elements

TREATMENTS

In a clinical trial the interest usually centers around one specific treatment. In many instances the treatment of interest is pharmacologic in nature, but also other interventions such as surgical treatments or therapeutic strategies may be studied. The treatment of interest is called the index treatment. It is contrasted to another treatment for comparison: the reference treatment. A newly developed drug may be contrasted to a placebo, a standard drug, or the absence of treatment. A surgical treatment is usually compared to the best available 'conservative' treatment. The choice of the reference treatment depends on the particular situation and is guided by considerations of internal validity (see further below).

DISEASE ENTITY

The inclusion and exclusion criteria of a trial must be viewed as the defining characteristics of the disease entity of interest. They specify the disease entity to which the treatments may be applied. According to Wulff, diseases are abstract categories in arbitrary classifications of patients[6]. However, abstract does not imply vagueness—the definition of the disease entity can (and should) be very specific.

The inclusion and exclusion criteria by themselves do not define a group of patients. The investigator must devise a recruitment scheme to obtain a group of patients to represent the disease entity. The recruitment scheme ties the selection of patients to a particular place (hospital, city, country) and to a particular time (period of patient accrual).

The HINT inclusion criteria, which are described in chapter 3, expressly define the syndrome of unstable angina (prolonged anginal pain at rest). The trial was carried out in Dutch patients presenting with this syndrome at one of the 11 participating hospitals between 1981 and 1984. Treatment effects as observed in these patients are of interest insofar as they provide a means to learn about treatment effects in unstable angina in general. The specificity of the definition of unstable angina as presented in chapter 3 applies to the (particularistic) patient group and to to the (abstract) disease entity as well. The disease entity as defined in HINT not only refers to a particular syndrome (unstable angina) but also to a specific phase in its development (i.e. as diagnosed immediately after relief of chest pain after admission to hospital).

The great majority of diseases present a clinical spectrum varying from mild to severe symptoms. The diagnostic characteristics themselves do not define the clinical spectrum. Tertiary referral centres see a disproportionate large proportion of high risk patients and, therefore, a clinical spectrum that can be quite different from what would have been obtained if the same criteria had been applied in the setting of a general practice[7]. The inclusion and exclusion criteria of a clinical trial define the disease entity to be studied, but various features of the recruitment procedure ultimately determine the clinical spectrum of the disease eventually studied. The baseline profile (as described by the distribution of baseline characteristics) and the clinical course in the reference group are essential additional descriptors of the clinical spectrum of the disease that is represented by the admitted patients.

OUTCOME

In every clinical trial treatment effects are invariably measured in terms of certain disease outcomes. The definition of the outcome is a major concern in the design of a study. In most clinical trials the outcome of interest is an (untoward) clinical event which may or may not occur over a fixed period of time (the outcome event). For example, in trials comparing secondary preventive measures after myocardial infarction one might choose death within two years as the outcome event. The outcome event in HINT is 'recurrent ischaemia or myocardial or myocardial infarction within 48 hours'.

With the outcome event specified, its occurrence can be identified for each individual patient. The proportion of patients who have developed the outcome event characterizes the occurrence in the whole group. The outcome is not necessarily the occurrence of an all-or-none event observed over a fixed follow-up period. For example, if the concern is with blood pressure, the change in diastolic blood pressure over the treatment period would constitute the outcome in individual patients. The mean or median change

in diastolic blood pressure would characterize the outcome in the whole group.

Internal Validity

Internal validity implies accurate effect measurement within the context of the clinical trial itself. Internal validity hinges on three issues: (1) Does the treatment comparison truly reflect the comparison of interest? (2) Are other factors which might influence the outcome equally distributed between the treatment groups? (3) Is the observation of the outcome identical between the treatment groups?

The conventional methods to achieve internal validity are: (1) the use of a placebo or sham treatment as reference treatment—to assure comparability of extraneous effects; (2) the use of random treatment assignment—to assure comparability of groups; (3) the use of blinding—to assure comparability of information[8]. These methods need not be used in all instances. Understanding of the rationale, however, provides guidance in designing an internally valid study.

COMPARABILITY OF EXTRANEOUS EFFECTS

The choice of the reference treatment is guided by an express understanding of what aspect of the index treatment is to be studied. In the assessment of drugs the attention is usually on the effect of the agent (chemical substance) itself. Possible placebo effects must be considered extraneous to the comparison at issue. Consequently, the drug is compared to placebo in order to eliminate (extraneous) placebo effect from the comparison. As regards surgery, one usually intends to compare the strategy of surgery with a strategy of conservative treatment. In this context, extraneous effects are irrelevant to the comparison. No sham operation is needed in the reference group. The need for a placebo treatment thus originates from the investigator's perception of what aspects of the index treatment must be considered extraneous to the comparison at issue.

COMPARABILITY OF GROUPS

The data will reflect the effect of the index treatment relative to the reference treatment only insofar as the two groups of patients are comparable. Comparability in this sense means that the expected occurrence of disease outcomes is the same for the compared groups had they been given the same treatment. The groups are required to have comparable prognosis. If no specific assignment scheme would have been devised (that is, in a nonexperimental study), comparability of groups is compromised by the treating physician's preference to assign the more seriously afflicted patients to the favoured or to the most intensive treatment. Perceived high risk or poor prognosis tends to constitute an indication for intervention[9]. In the context of a nonexperimental study, patients selected for different treatments have by definition different indications. Hence they cannot be expected to have comparable prognosis. This phenomenon (usually referred to as confounding by indication) poses major and often insurmountable difficulties to nonexperimental evaluation of efficacy. To achieve comparable groups, the investigator must devise an assignment scheme in advance that completely eliminates (intended or unintended) selection of patients into preferred treatment groups. Today, random allocation of patients to treatments is widely accepted as the method of choice[10,11]. It renders treatment assignment completely unpredictable and beyond control of the treating physician.

Systematic assignment schemes (e.g. in which every other patient is assigned to the index treatment) or schemes based on patient characteristics (e.g. based on the day of birth) implies that the treating physician knows the treatment assignment of a particular patient in advance. This prior knowledge may affect the physician's decision regarding entry or not, and treatment assignment becomes liable to manipulation. Systematic treatment assignment must therefore be rejected. A treatment assignment procedure based on randomisation but implemented in such a way that the physician has access to the randomisation code before the patient is definitively (and irrevocably) entered into the trial has the same deficiency.

In a double blind comparison of pharmacologic treatments a system of pre-packed medications to be issued sequentially to patients as they are entered into the trial usually suffices. In an open comparison of, for example, surgical treatment with continued pharmacologic treatment a system of registration by telephone upon which the next treatment assignment is issued is mandatory. The frequently used so-called envelope method usually provides no safeguard against manipulation.

Even procedurally flawless random assignment of treatments does not necessarily produce comparable groups of patients owing to random variation. As a consequence, comparability of prognosis remains a major concern in data analysis. A further discussion on this topic is provided in chapter 5.

COMPARABILITY OF INFORMATION

Information regarding outcomes in individual patients must be obtained in a way that is identical

for the treatment groups. The conventional way to assure comparability of outcome information has been blinded data collection. It is an essential feature of trials involving outcomes subject to interpretative observation. An alternative would be to choose a 'hard' outcome criterion, e.g. death within seven days of randomisation. This outcome does not allow any subjectivity from the observer, provided that information over the whole risk period for all patients is obtained. However, even if a 'hard' outcome is selected, blinding of the patient or the treating physician may be indicated to maintain comparability of extraneous effects, in particular with regard to prescription of additional treatment.

Precision

Observed effects in a clinical trial are subject to random variation. If the study is replicated in the same context, other treatment effects will be observed. Random variation is that part of the outcome one cannot predict. In the context of a clinical trial it originates from (1) the process of randomisation itself and (2) random events occurring during follow-up of individual patients. Precision pertains to random variation in the observed effect estimate.

The primary way to reduce the influence of random variation on the observed effect estimate (i.e. to increase precision) is to enlarge the size of the study. It is stressed that increased precision is only relevant if the trial design warrants internal validity.

It is a prevalent belief that required size of the treatment groups can be determined in advance by statistical methods. Indeed, given certain quantities one can calculate the required study size statistically. The basic line of thought underlying these calculations and the actual formulas can be found elsewhere[11–13]. The apparent exactness of these calculations creates the impression that the calculated study size is the optimal study size. This impression is delusive. Firstly, the study size is calculated from arbitrarily chosen statistical quantities, which include the level and the power of the test but also expected outcome occurrences, which are generally speaking unknown. Secondly, the calculations are extremely sensitive to these underlying assumptions: a small change in expected outcome occurrences may have a considerable impact on the required size. With all these arbitrary decisions and estimates, the number arrived at by calculation from formulas is subject to considerable manipulation. Thirdly, statistical size calculations are not based on any optimality criterion weighing the advantage of greater precision against the costs of performing a larger trial. In fact, the cost–benefit problem is insoluble, as the impact of even the most promising trial is unpredictable: one cannot know in advance how many patients will benefit from the trial findings. Fourthly, the calculations do not take account of other available evidence. As a result, one is left to choose the study size judgmentally in the light of one's best (intuitive) understanding of precision, costs, and a surmise of the utility of the result[8].

Generalization

Generalization may be viewed as the specification of a 'law of nature' which is believed to underlie the observations. For instance, from the many trials measuring the effect of beta blockers in acute myocardial infarction, one may infer the following 'law of nature': 'Beta blockers in suspected acute myocardial infarction reduce one-week mortality by 19%'. This statement does not only pertain to the patients that were entered into the particular trials. Rather, it confers a notion about a treatment effect in an abstract disease entity (suspected acute myocardial infarction, no contra-indication for a beta blocker). Scientific generalization is a process of abstraction from time- and space-specific empirical measurement of a treatment effect in a group of patients to a treatment effect in an (abstract) disease entity. Scientific generalization is not specific to medical research. It pertains to all branches of science. It has puzzled scientists and philosophers of science as well for centuries and is still not completely understood[10].

Scientific generalization in the context of clinical trials is judgmental as to which characteristics of the trial patients are relevant to generalization. As an example, from a clinical trial in men, one might generalize the results to women if gender is considered to be irrelevant to the treatment effect—a judgement based on knowledge about the likely mechanism of action and its relation to the patient's gender.

Scientific generalization (in the research setting) should not be confused with statistical generalization from sample to sampled population in sample surveys. Statistical generalization (e.g. in an opinion poll) does not go beyond the temporal and spatial constraints of the sampled population. For this reason it cannot be considered the basis for scientific generalization. As a matter of fact, if scientific generalization were simply a matter of statistical generalization, there would be no application to humans of results obtained from animal research[10].

The relevance of a particular trial is ultimately

determined by its potential for generalization: findings should support conclusions about the therapeutic benefit to be expected in a defined clinical indication which can be recognised in day-to-day clinical practice. A further discussion on this aspect of generalization is provided in the introductory notes to chapter 8.

Ethical aspects

The design and conduct of a clinical trial are fraught with ethical dilemmas. The general ethical requirements of clinical research have been formulated in the Declaration of Helsinki issued by the World Medical Association. It is widely accepted that patients must be fully informed of their participation in a trial and of the possible consequences and that participation may take place only after consent has been given.

A first premise is that it is unethical to conduct an experiment that is poorly designed or carried out. Further, a trial protocol is only ethically justifiable if under present knowledge there is no established explicitly better treatment available outside the protocol. Also, the treatment alternatives should be equally acceptable. In each clinical trial there is a potential conflict between the needs of the individual patient who requires treatment at that moment and the needs of future patients who might benefit from the research efforts to identify better treatments. Each trial requires a careful weighing of the needs of the individual against those of the collective. On the other hand, a patient entering a randomised trial with balanced allocation to either of two treatment regimens has a chance of one half of receiving the better treatment, a guarantee that cannot always be given in ordinary clinical practice.

The epidemiologic perspective of clinical trials

Clinical research may be viewed as applied medical science, or as the scientific link between biomedical science (basic research) and clinical practice (examination and treatment of the individual patient). The goal of all scientific research in medicine is to expand existing knowledge on disease and health in humans. The medical scientist, just like the physicist, seeks to expand knowledge of nature. In medical science, however, the quest for knowledge is not a goal in itself but derives from the desire to prevent diseases and to improve their treatment. This principle is, of course, very prominent in clinical research, but it applies to basic research as well.

In contrast to basic research, which is concerned with the functioning of the human organism in disease and health, clinical research deals with the occurrence of states and events of medical concern among patients under medical care. This facet has given rise to the concept and discipline of clinical epidemiology. The more traditional epidemiology studies the occurrence of an outcome or a health event (e.g. atherosclerotic coronary heart disease) in relation its determinants (e.g. cholesterol) in man. Likewise, the forcus of clinical epidemiologic research is on the relation between an outcome (e.g. recurrence of myocardial ischaemia) and a determinant (e.g. treatment with a calcium antagonist) among patients (e.g. patients admitted to hospital for unstable angina). 'Determinant' is used to indicate a characteristic on which the outcome depends, e.g. in the sense that cholesterol may 'determine' the occurrence of atherosclerotic heart disease, or that recurrence of ischaemia is 'determined' by the treatment that is used.

A multitude of medical sciences and areas of practice embody epidemiologic problems. Therefore, epidemiology does not constitute a field of knowledge per se[8]. Cardiovascular epidemiologic research, whether clinical, etiologic, or preventive, is research within the field of cardiology. The adjective epidemiologic relates to the form of the research problem: the occurrence of an outcome (or health event) in relation to one or more determinants in man. The form of the epidemiologic research problem is common to all fields of clinical medicine. The principles of studying the occurrence of illness and related states and events in man constitute what may be termed theoretical epidemiology[8]. Other terms that might be used are the theory of applied medical science, the theory of clinical research.

Epidemiology as a research discipline distinguishes two types of studies: experimental and nonexperimental. In an experimental study the investigator deliberately manipulates a condition in order to learn about its effect on outcome. Epidemiologic experiments have their roots in the concepts of scientific experimentation (e.g. in physics and agricultural science). When experiments are not feasible, nonexperimental studies (i.e. studies without artificial manipulation of the determinant) are designed to emulate what might have been learned had an experiment been conducted[10]. Epidemiologic research, whether experimental or non-experimental, is by definition empirical. It is based upon systematic collection of observations on the phenomena of interest in a defined group of individuals. The term 'observational' to indicate a nonexperimental epidemiologic study must be considered a misnomer.

Thus, a clinical trial may be defined as a scientific experiment with patients as subjects. In a scientific experiment the scientist varies one factor under otherwise controlled circumstances, in order to ascertain what effect variation in that factor would have on the outcome of interest. In physical sciences the scientist usually can control all other factors that would affect the outcome. Complete control of other factors affecting the outcome cannot be achieved in the setting of clinical medicine, but techniques such as placebo treatment, randomisation, and blinding are available to establish conditions for valid experimentation.

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3 Formation of the HINT cohort

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Design and methods

INITIAL SCREENING OF PATIENTS

At admission to hospital men and women under 71 years of age in whom unstable angina was suspected were screened for inclusion before the results of the enzyme measurements were known. Chest pain (if present) was treated according to a standardized protocol (see below). Eligibility was assessed only after relief of chest pain. Eligibility could also be assessed when chest pain developed after admission to hospital. No logbook of screened but eventually rejected patients was kept.

TREATMENT OF ANGINA PAIN

Chest pain was treated with sublingual glyceryl trinitrate (maximum two 1·0 mg doses) and if it persisted for more than five minutes with an intravenous injection of glyceryl trinitrate (maximum 1 mg in 10 ml 5% glucose) or fentanyl (0·05 mg). Electrocardiograms were recorded before treatment was started, between each of the above steps, and after relief of pain. Blood samples were obtained after relief of pain. If chest pain could not be relieved by these treatments, a provisional diagnosis of suspected acute myocardial infarction was made, and further measures were left to the discretion of the treating physician.

At the time when the trial was started, the study protocol had no provision for the intravenous injections. The patient should chew one 10 mg dose of nifedipine if chest pain was not relieved by sublingual glyceryl trinitrate. From 1 January 1982 nifedipine was disallowed, and the study protocol required intravenous injections with glyceryl trinitrate or fentanyl if sublingual glyceryl trinitrate failed to relieve chest pain.

ELIGIBILITY

To qualify for admission to the trial the presence of either of the following was required: (1) a chest pain episode in the hospital accompanied by a varying pattern of ST-segment or T-wave changes suggesting reversible myocardial ischaemia; (2) a history of typical angina at rest or during light activity occurring within 12 hours of admission and lasting more than 15 minutes combined with either ST-segment or T-wave abnormalities, a documented history of myocardial infarction or unstable angina, or at least 50% narrowing of a major coronary artery observed at earlier angiography.

Patients who did not qualify at hospital admission were included on the basis of the above criteria when chest pain subsequently developed, provided that available enzyme values were below twice the local upper normal limit.

If chest pain was not relieved by the above treatments or if the patient impressed otherwise as sustaining acute myocardial infarction, the patient qualified as yet when serial enzyme measurements showed that myocardial necrosis was absent, provided that chest pain had subsided and that no time limits were exceeded.

Patients were not included if a contra-indication for treatment with a beta blocker or nifedipine was present (clinically overt heart failure, heart rate below 50 beats min^{-1}, or systolic blood pressure <100 mmHg) or if an indication for treatment with a beta blocker or nifedipine was present (heart rate over 120 beats min^{-1} or systolic blood pressure >170 mmHg and diastolic blood pressure >110 mmHg). Also excluded were patients with a possible noncoronary cause of angina pectoris, such as anaemia (haemoglobin $<6{\cdot}5$ mmol l^{-1}), conduction abnormalities other than bundle branch block, congenital or valvular heart disease, cardiomyopathy, serious pulmonary disease. Patients with new Q-wave formation in the electrocardiogram or with acute myocardial infarction within the last week were not included. In addition the following exclusions were applied: maintenance treatment with nifedipine, age over 70, serious noncardiac disease, and previous participation in HINT.

If patients had high heart rate or high blood pressure immediately after admission to hospital, enrolment should proceed but heart rate and blood pressure were required not to exceed the above limits just before randomisation.

INFORMED CONSENT

It was the responsibility of the treating physician to inform possible participants of the trial and to ask consent. The information was intended to give each participant a thorough understanding of the purpose and the nature of the trial, the cooperation required,

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and any side-effects possibly associated with the trial medication regimens. The benefits the patient might derive from the trial and the impact possibly emerging from the trial were explained. It was clearly pointed out that the patient might be treated with placebo, but also that placebo treatment might emerge as the most favorable treatment in the trial. It was expressly stated that the patient was completely free to refuse and that if he did so he would receive standard treatment with the same degree of care. It was also pointed out that the trial medication consisted of four-hourly doses, so that awakening during the night in order to take medication was necessary.

To assist the treating physician, a sample consent form was made available. Only oral consent was required. If possible, relatives of the patients attended the information and consent session. If no relatives were available, consent was asked in the presence of a nurse. If the patient desired some time for reflection, this was granted. The informed consent procedure was approved by the institutional review boards of the participating Clinical Centres. Modifications required by the institutional review board were applied in the centres concerned. These included, amongst others, that an information pamphlet was handed over to possible participants.

The consent also included permission for the Coordinating Centre to gather information on the clinical course for the sole purpose of scientific research. Whether the consent also included permission for subsequent coronary angiography depended on the angiography policy in the Clinical Centre. If angiography was part of the diagnostic routine, permission for angiography was asked in the context of this routine. If this was not the case, permission to perform angiography was incorporated in the consent for the trial.

LATE EXCLUSIONS

The informed consent procedure and administrative procedures of admission to hospital sometimes caused a considerable delay, in which conditions could have changed. It was required that all criteria still applied at randomisation and that no more than 12 hours had elapsed since the last episode of chest pain. In particular, a patient was as yet excluded if signs of acute myocardial infarction had developed before the start of trial medication: renewed chest pain that could not be relieved as described above, new Q-wave formation on the electrocardiogram, enzyme rises over twice the local upper limit for normal. (There was no need to wait until enzyme values were returned from the laboratory, but already available measurements were taken into account). If the treating physician came to the conclusion that the clinical condition of the patient had deteriorated too much, the patient was also excluded.

START OF TRIAL MEDICATION

As soon as eligibility was established and informed consent was obtained the following was undertaken: (1) an electrocardiogram was recorded (the baseline electrocardiogram), (2) blood samples were obtained (for the determination of enzyme concentrations, chemistry, haematology, plasm levels of nifedipine and metoprolol), (3) baseline measurements of heart rate and blood pressure were taken, in duplicate ten minutes apart. Thereupon, trial medication, which was available at the coronary care unit in pre-packed sequentially numbered boxes, was started without further delay. The moment of randomisation was defined as the moment when the first dosage of trial medication was taken.

Definition of the HINT cohort

The enrolment procedure as carried out in the Clinical Centres has yielded a cohort of patients to be followed onwards from randomisation. To promote clarity of data description and data analysis, all enrolments were retrospectively grouped as 'unassessable', 'improper', or 'proper'. The grouping was applied by the Classification Committee (see chapter 6) based upon pre-randomisation data only.

An enrolment was grouped as unassessable if any of the following applied: (1) loss of all or most of the electrocardiograms; (2) inability to identify the moment of randomisation—an uncertainty margin not greater than one hour was allowed; (3) inability to identify the randomisation number for a particular patient. Second enrolments were also counted in this category.

Enrolments in which the inclusion protocol had been unequivocally violated were grouped as improper under the following headings: (1) misinterpretation of recent history: a delay of more than 12 hours between the last attack of chest pain and randomisation, duration of chest pain at home less than 15 minutes, angina of effort only, misidentification of previous maintenance treatment with a beta blocker; (2) overlooked exclusion criteria: too old, hypertension, bradycardia, recent myocardial infarction, unequivocal electrocardiographic signs of evolving acute myocardial infarction; (3) use of unallowed medications before randomisation, either to treat anginal pain (chewing a capsule nifedipine,

opiates) or otherwise (an infusion of glyceryl trinitrate, intravenous beta blockade); (4) persisting chest pain at randomisation; (5) miscellaneous. A protocol violation constituted entry of an ineligible patient. This was mostly a matter of mismanagement of the trial protocol, often obvious and clearly preventable but sometimes of a more subtle kind. Take as an example a patient who qualified for admission on the basis of transient ST-segment changes during an episode of chest pain after hospital admission. Consent was granted after a delay of two hours. In keeping with the instructions, the nurse recorded an electrocardiogram just before start. The electrocardiogram showed distinct new Q-wave formation: an exclusion criterion had eventually been overlooked.

The remaining patients (i.e., those with assessable records, without unequivocal violations of the admission protocol) were grouped as proper; they constitute the HINT cohort.

Central review of the electrocardiograms

The Classification Committee reviewed all pre-randomisation electrocardiograms to ascertain the required ST-segment or T-wave changes or abnormalities.

For patients enrolled on the basis of purported ST-segment or T-wave changes during pain the Classification Committee could either (1) confirm the (required) ST-segment or T-wave changes; (2) acknowledge steady ST-segment or T-wave abnormalities; or (3) deny any ST-segment or T-wave abnormality. If only one electrocardiogram recorded during pain was available, changes could by definition not be established. The case was then classed under (2) or (3) of the above.

For patients enrolled on the basis of a recent history of chest pain at home and additional evidence for atherosclerotic coronary heart disease the Classification Committee ascertained the evidence: ST-segment or T-wave abnormalities, previous myocardial infarction as evidenced from hospital case notes or Q-waves on the electrocardiogram, previous episodes of unstable angina as evidenced from hospital case notes and serial electrocardiograms, or angiographically shown narrowings of the coronary arteries reported at earlier angiography.

The goal of the Classification Committee's review was to put the enrolments in order for data presentation and data analysis. Consequently, the review of the Classification Committee did not necessarily follow the momentary reasoning of the treating physician when the patient was admitted. Take as an example a patient who came to the emergency room after an attack of chest pain at home which had subsided spontaneously before arrival at the hospital. The admission electrocardiogram showed T-wave inversion in V_3 and V_4. The treating physician (rightly) decided that the patient was eligible for immediate enrolment. However, the electrocardiogram showed no ST-segment or T-wave changes when the patient subsequently developed renewed chest pain during the consent procedure. The patient was classified on the basis of the later in-hospital attack of chest pain, and the (required) ST-segment or T-wave changes were not confirmed.

The Classification Committee took a mild posture when assessing ST-segment or T-wave changes or abnormalities. Minute changes or abnormalities sufficed. No complete return to normality after relief of chest pain was required. If worsening ST-segment or T-wave abnormalities unequivocally pointed towards evolving myocardial infarction, the enrolment was grouped as improper.

Also, the presence of Q-waves greater than 0·03 seconds or Q-wave equivalents (R-wave $>0{\cdot}03$ seconds in V_1 and R/S-ratio greater than unity in V_2) on pre-randomisation electrocardiograms was ascertained.

Definition of recorded baseline characteristics

CLINICAL HISTORY

The presence of angina pectoris prior to admission to hospital was scored in: (1) no angina pectoris, (2) angina pectoris of effort present for less than four weeks, (3) angina pectoris of effort present for more than four weeks with gradual acceleration during the last few days or weeks, (4) stable angina pectoris of effort present for more than four weeks, without any acceleration prior to the presenting episode of angina at rest.

Previous myocardial infarction was ascertained from clinical case notes and from the presence of Q-waves on the admission electrocardiogram. Results of previous angiography were recorded from angiography reports. The left main, the left anterior descending, the circumflex, and the right coronary artery were scored as diseased if the report made mention of a narrowing of at least 50% in the artery itself or in any of the main branches (first or second diagonal for the left anterior descending artery, first to third marginal branch for the circumflex artery, descending posterior for the right coronary artery—irrespective of its origin). The most recent angiogram was used. An artery with a bypass was scored as

diseased. In addition, previous bypass surgery was recorded. Medications being taken prior to admission to hospital were recorded in the following categories: beta blockers, long-acting oral nitrates, oral anticoagulants, diuretics, cardiac glycosides, antiarrhythmic drugs, calcium antagonists other than nifedipine, platelet aggregation inhibiting drugs, antihypertensive drugs. Furthermore, medications being taken for pain relief after hospital admission but before randomisation were recorded in the following categories: sublingual glyceryl trinitrate, an intravenous injection with glyceryl trinitrate or fentanyl.

TIME DELAYS

The pain free interval was defined as the time elapsed between pain relief after the last episode of chest pain and randomisation. The pain free interval represents the period over which the patient has been clinically stable.

The moment of qualification was taken as the moment when eligibility could have been established, i.e. for patients with in-hospital episodes of chest pain with ST-segment or T-wave changes: after the last episode of chest pain with ST-segment or T-wave changes; for patients with in-hospital episodes of chest pain without ST-segment or T-wave changes: after the last attack of chest pain; for patients without in-hospital episodes of chest pain: the time of admission to hospital. The randomisation delay was defined as the time elapsed between qualification and randomisation. The randomisation delay represents the delay due to the informed consent procedure and further unnecessary delays between qualification and randomisation.

The hospital delay was taken as the time interval between hospital admission and randomisation.

PRE-RANDOMISATION ELECTROCARDIOGRAPHY

For each patient two electrocardiograms recorded before randomisation were singled out for further analysis: an electrocardiogram recorded in the absence of pain (the baseline electrocardiogram) and an electrocardiogram made during pain (the pain electrocardiogram), the latter only for patients with pain while in hospital.

The last pre-randomisation electrocardiogram obtained in the absence of pain was taken as the baseline electrocardiogram. If no electrocardiogram recorded in the absence of pain was available, an electrocardiogram made after substantial diminution of pain was taken as baseline electrocardiogram. When only electrocardiograms made during unabated chest pain were available, the baseline electrocardiogram was considered not available.

The pain electrocardiogram was selected by one cardiologist as the electrocardiogram made during pain that most clearly presented the abnormalities that were typical for myocardial ischaemia. The cardiologist was blinded to the patient's trial medication assignment. Electrocardiograms made while chest pain was still untreated were preferred. The pain electrocardiogram was not available for patients admitted on the basis of a chest pain episode at home.

Both electrocardiograms were submitted for systematic coding of abnormalities. If the coding technician decided that an electrocardiogram could not be coded owing to the poor quality of the electrocardiogram, it was, if possible, replaced by another electrocardiogram. The electrocardiograms were coded for the Minnesota code[1], the cardiac infarction injury score[2], and a specially developed ST-segment score[3]. The latter recorded (amongst other things) the maximal amount of ST-segment depression and the maximal amount of ST-segment elevation in the following four groups of leads: infero-posterior (leads II, III, aVF), anterior (leads V_3–V_5), V_2 (lead V_2 only), and lateral (leads I, aVL, V_6). The coding was in the following categories: none, 0·01–0·04 mV, 0·05–0·09 mV, 0·10–0·19 mV, 0·20–0·50 mV, 0·51 mV or more. The scores were declared missing (1) if the electrocardiogram was not available, (2) if the electrocardiogram was illegible (and could not be replaced by a suitable legible one), or (3) if any of the Minnesota codings rendered the ST-segment undefined (codes 6-4-1, 7-1-1, 7-2-1, 7-4, or 9-8-1).

Several electrocardiographic baseline characteristics were derived from the codes. The main principle was to describe abnormalities present on the baseline electrocardiogram and changes in the pain electrocardiogram relative to the baseline electrocardiogram. Separate codes were used to indicate that the baseline or the pain electrocardiogram was missing. The latter circumstance is of clinical relevance because this would occur if the patient had arrived at the hospital after chest pain had subsided. The presence of ST-segment depression of at least 0·1 mV on the baseline electrocardiogram was based upon the maximal ST-segment depression coded for the four groups of leads. The presence of ST-segment elevation on the baseline electrocardiogram was defined analogously. More ST-segment depression during pain was considered to be present if the ST-segment coding for any of the four groups of leads was in a higher category at pain than at baseline. More ST-segment elevation during pain

was defined analogously. These variables were declared missing (1) if the pain electrocardiogram was missing, (2) if its ST-segment was undefined, (3) if the baseline electrocardiogram was missing, or (4) if its ST-segment was undefined.

HEART RATE AND BLOOD PRESSURE

Two measurements of heart rate and of systolic and diastolic blood pressure were scheduled for each patient. Baseline values for heart rate and for blood pressure were taken as the average of the two measurements, provided that they were not more than fifteen minutes apart. Otherwise, the last measurement of heart rate and systolic and diastolic blood pressure was taken as the baseline value. If more than four hours had elapsed between the last measurement and randomisation or if there were no measurements at all, the baseline values were considered missing.

ACTIVITIES OF CARDIAC ENZYMES

Blood samples for measurements of activities of creatine kinase or its MB-isoenzyme and glutamic oxaloacetic transaminase were obtained at least once (and preferably shortly) before randomisation. All enzyme determinations were performed locally and were subsequently related to local normal values. They are expressed as a percentage of the local upper limit for normal. (Values over 200%—that is, activities over twice the local upper limit for normal—are referred to as significantly raised.)

The last enzyme values obtained before randomisation were taken as the baseline values for the above enzymes, provided that had been obtained no longer than six hours before randomisation. Post-randomisation values were never taken as baseline value.

Description of the HINT cohort

RESPECTIVE CATEGORIES OF ENROLMENT

Thirty enrolments were classified as unassessable. In three patients all electrocardiograms were missing. The moment of randomisation could not be identified in four patients. For two patients the randomisation number could not be identified. There were seven second enrolments. Fourteen patients developed a contra-indication after they had provisionally been assigned a randomisation number but before trial medication was actually started.

Between 1 February 1981 and 30 October 1984, 668 patients with assessable records were enrolled in 11 Clinical Centres. Not all Clinical Centres participated over the whole accrual period. Table 3.1 shows the contribution per Clinical Centre. Figure 3.1 shows patient accrual over time.

Table 3.1 Patient accrual per clinical centre

Patients entered	668
Free University Hospital, Amsterdam	90 (13%)
Academic Medical Centre, Amsterdam	66 (10%)
Catharina Hospital, Eindhoven	34 (5%)
University Hospital, Groningen	7 (1%)
Leyenburg Hospital, The Hague	143 (21%)
Sint Lambertus Hospital, Helmond	41 (6%)
University Hospital, Leyden	82 (12%)
Sint Annadal Hospital, Maastricht	13 (2%)
Radboud Hospital, Nijmegen	32 (5%)
Thoraxcenter University Hospital, Rotterdam	110 (16%)
University Hospital, Utrecht	50 (8%)

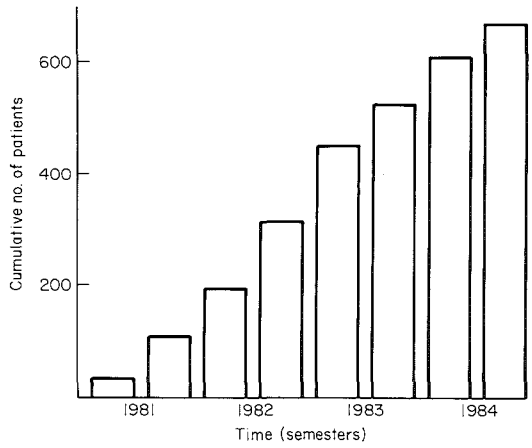

Figure 3.1 Patient accrual over time.

Table 3.2 shows the occurrence of unequivocal violations of the enrolment protocol in 131 patients. The Classification Committee decided that fourteen patients showed unequivocal explicit signs of evolving myocardial infarction on pre-randomisation electrocardiograms. In some patients more than one protocol violation occurred. The remaining 537 patients were eligible and thus constitute the HINT cohort.

PROFILE OF THE HINT COHORT

Table 3.3 shows the baseline values for the activities of the cardiac enzymes. Twenty-two patients had significantly raised baseline values for at least one cardiac enzyme (a value greater than 200%). In another three patients significantly raised enzyme values were registered, but these were considered of noncardiac origin: raised activities of glutamic oxaloacetic transaminase in one patient who was an

Table 3.2 Patients in whom an unequivocal violation of the admission protocol occurred

Patients with violation of admission protocol	131
Misinterpretation of recent history	32 (24%)
> 12 hours pain free	22 (17%)
Pain < 15 min	4 (3%)
Angina of effort	3 (2%)
Previous beta blockade	5 (4%)
Overlooked exclusion criteria	49 (37%)
Age > 70	2 (2%)
Hypertensive	3 (2%)
Hypotensive	6 (5%)
Tachycardia	1 (1%)
Bradycardia	9 (7%)
Overt signs of heart failure	2 (2%)
Conduction abnormalities	2 (2%)
Valvular heart disease	8 (6%)
Serious pulmonary disease	3 (2%)
Recent myocardial infarction	1 (1%)
Evolving myocardial infarction *	14 (11%)
Previous maintenance nifedipine	1 (1%)
Unallowed medications	52 (40%)
To treat chest pain †	40 (31%)
Infusion of glyceryl trinitrate	5 (4%)
Other	7 (5%)
Persisting chest pain at randomisation	6 (5%)
Other	1 (1%)

* Unequivocal signs of evolving myocardial infarction on pre-randomisation electrocardiograms.
† These include opiates and chewing a capsule of nifedipine. In some patients more than one protocol violation occurred.

Table 3.3 Baseline values for the activities of three selected cardiac enzymes

	Cardiac enzymes			
	CK (N = 353)	MB–CK (N = 252)	GOT (N = 488)	Maximum (N = 520)
< 100% *	310 (88%)	224 (89%)	450 (92%)	448 (86%)
100–150%	19 (5%)	7 (3%)	23 (5%)	32 (6%)
150–200%	10 (3%)	7 (3%)	12 (2%)	18 (3%)
> 200%	14 (4%)	14 (6%)	3 (1%)	22† (4%)

CK, creatine kinase: MB–CK, MB-isoenzyme of creatine kinase; GOT, glutamic oxaloacetic transaminase; Maximum, maximum of these three enzymes;
* Activities at baseline are expressed as percentages of the local limit for normal.
† These 22 patients (4%) had a pre-randomisation myocardial infarction, which was not known when the patient was randomised.
In 17 patients, no pre-randomisation enzyme values were available.

alcoholic and two measurement errors. These enzyme values are not included in Table 3.3. The HINT cohort is described for patients with pre-randomisation myocardial infarction and those without separately.

Of the 515 patients without pre-randomisation myocardial infarction 177 (34%) were on previous maintenance treatment with a beta blocker. They are further described for the two groups defined by previous maintenance treatment with a beta blocker separately.

Table 3.4 shows the results of the central review of pre-randomisation electrocardiography. The treating physician's judgement on the presence of (qualifying) ST-segment or T-wave changes was confirmed in 80% of the patients without pre-randomisation myocardial infarction admitted on the basis an in-hospital episode of chest pain with accompanying electrocardiograms; in 7% of these patients the Classification Committee found no abnormalities at all. ST-segment or T-wave abnormalities at baseline were confirmed in 72% of the patients without pre-randomisation myocardial infarction enrolled on the basis of an episode of chest pain at home; in 15% other evidence of atherosclerotic coronary heart disease was available; in the remaining 13% no further evidence for atherosclerotic coronary heart disease was available.

Table 3.5 shows selected demographic clinical baseline characteristics of the patients of the HINT cohort. The vast majority of HINT patients was of the male gender and between 50 and 65 years of age. The majority of patients had a history of angina pectoris, but not of previous myocardial infarction. Among the patients on previous maintenance treatment with a beta blocker there was a (relatively) higher prevalence of previous angina pectoris and previous myocardial infarction; angiography and bypass surgery had also been performed more often in these patients.

Table 3.6 shows medications being taken before hospital admission. Previous maintenance treatment with a beta blocker consisted mostly of metoprolol or propranolol. Long-acting nitrates were being taken by 100 patients (19%). Antiarrhythmic drugs or cardiac glycosides were taken by only a few patients. Diuretics were being taken by 100 patients (19%), mostly for hypertension. Table 3.6 also shows medications given for pain relief prior to randomisation. Sublingual glyceryl trinitrate sufficed in almost all patients.

Table 3.4 Review of pre-randomisation electrocardiographic abnormalities by the Classification Committee

	Pre-randomisation MI		Previous beta blockade	
	Yes (N = 22)	No (N = 515)	No (N = 338)	Yes (N = 177)
Pain ECGs available	19	319	210	109
ST–T changes confirmed	17 (90%)	254 (80%)	172 (82%)	82 (75%)
Steady ST–T abnormalities	2 (10%)	41 (13%)	21 (10%)	20 (18%)
No ST–T abnormalities	0 (0%)	24 (7%)	17 (8%)	7 (6%)
Pain ECGs not available	3	196	128	68
Resting ST–T abnormalities	2 (67%)	141 (72%)	90 (70%)	51 (75%)
Other evidence of ACHD	1 (33%)	29 (15%)	18 (14%)	11 (16%)
Neither of the above	0 (0%)	26 (13%)	20 (16%)	6 (9%)

MI, myocardial infarction; ECGs, electrocardiograms; ST–T, ST-segment or T-wave, ACHD, atherosclerotic coronary heart disease.
Pain electrocardiograms (i.e. electrocardiograms recorded during chest pain) were, generally speaking, only available for patients with chest pain while in hospital. Changes refer to ST-segment or T-wave changes between electrocardiograms obtained during pain and electrocardiograms obtained after relief of chest pain.

Table 3.7 shows the pain free interval, the randomisation delay, and the delay in the hospital. Trial medication was started after a pain free interval of less than one hour in 26% of patients and in a further 37% after an interval of between one and three hours. In 68% of patients there was an (unwanted) delay of more than one hour between qualification and randomisation. Only 12% of patients were randomised within one hour of hospital admission.

Table 3.8 shows characteristics from the (pain free) baseline electrocardiogram. ST-segment codings were not available in 22 patients: in five patients no codable pre-randomisation baseline electrocardiogram was available, in 8 patients only (one) electrocardiogram made during pain was available, and in nine patients ST-segments were undefined because of Minnesota code incompatibilities (e.g. a bundle branch block). ST-segment depressions of at least 0·1 mV at baseline were present in 98 patients (18%), ST-segment elevations of at least 0·1 mV in 109 patients (20%).

Table 3.9 shows electrocardiographic baseline characteristics from the pain electrocardiogram. ST-segment codings during pain were not available in 199 (37%) patients, because they had not suffered chest pain while in hospital; in another 17 patients (3%) ST-segment codings were not available owing to illegibility of pain electrocardiograms or to Minnesota code incompatibilities. ST-segment depressions of at least 0·1 mV on electrocardiograms made during pain were present in 127 patients (24%); similar ST-segment elevations in 72 patients (13%). The codings of the ST-segment on the baseline electrocardiogram could be compared to those on the pain electrocardiogram in 308 patients (57%): more ST-segment depression occurred in 169 patients (31%), more ST-segment elevation in 107 patients (20%), whereas more ST-segment depression in some leads and more ST-segment elevation in other leads occurred in 53 patients (10%).

Table 3.10 shows baseline values for heart rate and blood pressure. Heart rates were lower for patients on previous maintenance treatment with a beta blocker in comparison to those not on beta blockers. Blood pressures were approximately equal for these groups of patients.

Discussion

According to one widely accepted definition patients who have recent onset (effort) angina, worsening angina, or angina at rest are classified as having unstable angina provided there are no signs of acute myocardial infarction[5]. It is generally recognised that the differential diagnosis of such cases may be difficult and that myocardial infarction may already have occurred or may be about to occur. In

Table 3.5 Selected demographic and clinical baseline characteristics

	Pre-randomisation MI		Previous beta blockade	
	Yes ($N = 22$)	No ($N = 515$)	No ($N = 338$)	Yes ($N = 177$)
Age				
30–54	7 (32%)	183 (36%)	133 (39%)	50 (28%)
55–61	11 (50%)	171 (33%)	108 (32%)	63 (36%)
62–70	4 (18%)	161 (31%)	97 (29%)	64 (36%)
Sex				
Male	20 (91%)	387 (75%)	253 (75%)	134 (76%)
Female	2 (9%)	128 (25%)	85 (25%)	43 (24%)
Previous infarction				
No	14 (64%)	322 (63%)	229 (68%)	93 (53%)
History only	3 (14%)	64 (12%)	35 (10%)	29 (16%)
Q-waves	5 (23%)	129 (25%)	74 (22%)	55 (31%)
History of angina *				
No	8 (36%)	143 (28%)	115 (34%)	28 (16%)
< 1 month	5 (23%)	165 (32%)	120 (35%)	45 (25%)
> 1 month, crescendo	5 (23%)	114 (22%)	56 (17%)	58 (33%)
> 1 month, sudden	4 (18%)	93 (18%)	47 (14%)	46 (26%)
Previous angiography				
No	20 (91%)	434 (84%)	306 (91%)	128 (72%)
Yes:	2 (9%)	81 (16%)	32 (9%)	49 (28%)
No coronary abnormalities	—	1 (1%)	1 (3%)	—
One vessel disease	—	31 (38%)	15 (47%)	16 (33%)
Two vessel disease	—	22 (27%)	6 (19%)	16 (33%)
Three vessel disease	2	23 (28%)	8 (25%)	15 (31%)
Left main disease	—	4 (5%)	2 (6%)	2 (4%)
Previous bypass surgery				
No	22	481 (93%)	321 (95%)	160 (90%)
Yes	—	34 (7%)	17 (5%)	17 (10%)

MI, myocardial infarction.
* Crescendo, angina pectoris of effort present for more than one month with gradual acceleration; sudden, angina pectoris of effort present for at least one month without any acceleration prior to the presenting episode of angina at rest.

the present trial 537 patients were enrolled in whom unstable angina was diagnosed at admission to the coronary care unit. This diagnosis was based on a combination of findings—prolonged chest pain at rest, evidence for causal myocardial ischaemia, and absence of signs of acute myocardial infarction such as chest pain refractory to treatment with nitrates or fentanyl or characteristic electrocardiographic signs. Unstable angina according to the HINT criteria is a subcategory of unstable angina as defined above. This diagnosis may also be viewed a subcategory of syndromes of prolonged chest pain at rest leading to admission to a coronary care unit, the diagnosis of suspected acute myocardial infarction being another subcategory. Many patients who are admitted to a coronary care unit have symptoms and signs in between those typical for unstable angina (i.e. reversible ischaemia) and those typical for acute myocardial infarction (i.e. irreversible ischaemia). The HINT patients specifically represent one end of the clinical spectrum; they have a low probability of evolving myocardial infarction at the moment of diagnosis. In 4% (22 out 537) myocardial infarction had already developed to the extent that enzyme activities were

Table 3.6 Medication being taken at hospital admission

	Pre-randomisation MI		Previous beta blockade	
	Yes (N = 22)	No (N = 515)	No (N = 338)	Yes (N = 177)
Maintenance treatments				
None	15 (68%)	294 (57%)	241 (71%)	53 (30%)
Beta blockers	4 (18%)	177 (34%)	—	177
Nitrates	—	100 (19%)	26 (8%)	74 (42%)
Anticoagulants	3 (14%)	76 (15%)	31 (9%)	45 (25%)
Diuretics	4 (18%)	96 (19%)	42 (12%)	54 (31%)
Cardiac glycosides	—	17 (3%)	9 (3%)	8 (5%)
Antiarrhythmic drugs	—	5 (1%)	5 (1%)	—
Calcium antagonists*	—	5 (1%)	4 (1%)	1 (1%)
Antiplatelet drugs	1 (5%)	16 (3%)	13 (4%)	3 (2%)
Other antihypertensives	3 (14%)	37 (7%)	13 (4%)	24 (14%)
Treatments for pain relief†				
No pain	2 (9%)	187 (36%)	122 (36%)	65 (37%)
Spontaneous	2 (9%)	34 (7%)	20 (6%)	14 (8%)
Glyceril trinitrate sl	17 (77%)	272 (53%)	177 (52%)	95 (54%)
Glyceril trinitrate or fentanyl iv	1 (5%)	22 (4%)	19 (6%)	3 (2%)

MI, myocardial infarction; sl, sublingual; iv, intravenous.
* Other than nifedipine, † given after hospital admission.

Table 3.7 Time delays before randomisation

	Pre-randomisation MI		Previous beta blockade	
	Yes (N = 22)	No (N = 515)	No (N = 338)	Yes (N = 177)
Pain free interval				
<1 hour	4 (18%)	133 (26%)	89 (26%)	44 (25%)
1–3 hours	12 (55%)	186 (36%)	121 (36%)	65 (37%)
>3 hours	6 (27%)	196 (38%)	128 (38%)	68 (38%)
Randomisation delay				
<1 hour	3 (14%)	167 (32%)	112 (33%)	55 (31%)
1–3 hours	14 (64%)	234 (45%)	154 (46%)	80 (45%)
>3 hours	5 (23%)	114 (22%)	72 (21%)	42 (24%)
Hospital delay				
<1 hour	1 (5%)	63 (12%)	43 (13%)	20 (11%)
1–3 hours	9 (41%)	240 (47%)	162 (48%)	78 (44%)
>3 hours	12 (54%)	212 (41%)	133 (39%)	79 (45%)

MI, myocardial infarction; pain free interval, time between relief of chest pain and randomisation; randomisation delay, delay between qualification and randomisation; hospital delay, time between hospital admission and randomisation.

Table 3.8 Baseline characteristics from electrocardiogram when pain absent

	Pre-randomisation MI		Previous beta blockade	
	Yes (N = 22)	No (N = 515)	No (N = 338)	Yes (N = 177)
ST-segment depression at baseline				
None	7 (32%)	214 (42%)	155 (46%)	59 (33%)
0·01–0·04 mV	4 (18%)	69 (13%)	52 (15%)	17 (10%)
0·05–0·09 mV	4 (18%)	119 (23%)	72 (21%)	47 (27%)
0·10–0·19 mV	1 (5%)	68 (13%)	32 (10%)	36 (20%)
0·20–0·50 mV	4 (18%)	25 (5%)	13 (4%)	12 (7%)
ST-segment code missing	2 (9%)	20 (4%)	14 (4%)	6 (3%)
ST-segment elevation at baseline				
None	4 (18%)	100 (19%)	64 (19%)	36 (20%)
0·00–0·04 mV	7 (32%)	127 (25%)	89 (26%)	38 (21%)
0·05–0·09 mV	4 (18%)	164 (32%)	110 (33%)	54 (31%)
0·10–0·19 mV	5 (23%)	91 (18%)	54 (16%)	37 (21%)
0·20–0·50 mV	—	13 (2%)	7 (2%)	6 (3%)
ST-segment code missing	2 (9%)	20 (4%)	14 (4%)	6 (3%)
T-wave inversion at baseline				
Upright	8 (36%)	145 (28%)	109 (32%)	36 (20%)
0·01–0·09 mV	7 (32%)	149 (29%)	102 (30%)	47 (27%)
0·10–0·50 mV	7 (32%)	192 (37%)	109 (32%)	83 (47%)
>0·50 mV	—	24 (5%)	15 (4%)	9 (5%)
T-wave code missing	—	5 (1%)	3 (1%)	2 (1%)
ST–T abnormalities at baseline*				
None	13 (59%)	269 (52%)	191 (57%)	78 (44%)
T-wave inversion only	2 (9%)	121 (23%)	78 (23%)	43 (24%)
ST non-anterior	—	18 (4%)	9 (3%)	9 (5%)
ST anterior	5 (23%)	87 (17%)	46 (14%)	41 (23%)
ST-segment code missing	2 (9%)	20 (4%)	14 (4%)	6 (3%)
CIIS-score at baseline				
<9	4 (18%)	161 (31%)	115 (34%)	46 (26%)
9–20	5 (23%)	161 (31%)	96 (28%)	65 (37%)
>20	11 (50%)	172 (33%)	113 (33%)	59 (33%)
Missing	2 (9%)	21 (4%)	14 (4%)	7 (4%)

MI, myocardial infarction: ST–T, ST-segment or T-wave, CIIS, cardiac infarction injury score.

* T-wave inversion, T-wave inversion of at least 0·10 mV; ST nonanterior, ST-segment depression or elevation of at least 0·10 mV in nonanterior leads only; ST anterior, ST-segment depression or elevation of at least 0·10 mV in anterior leads (V_2–V_5).

over twice the normal limit. These cases of pre-randomisation myocardial infarction could have been diagnosed immediately had instantaneous laboratory measurements been available. They form a special group of patients who are, by definition, no longer at risk for developing myocardial infarction in the follow-up period.

Of 515 patients without pre-randomisation myocardial infarction 93 (18%) had at least 0·10 mV ST-segment depression at baseline, and of 303 patients with pain while in hospital 118 (39%) had at least 0·1 mV ST-segment depression during pain. The percentages for ST-segment elevation were 20% and 22%, respectively. These findings confirm the clinical impression that patients whose electrocardiographic signs impressed as particularly ominous while still indicative of reversible ischaemia were generally withheld from the trial.

Table 3.9 Baseline characteristics from electrocardiogram when pain present

	Pre-randomisation MI		Previous beta blockade	
	Yes (N = 22)	No (N = 515)	No (N = 338)	Yes (N = 177)
ST-segment depression during pain				
No in-hospital pain	3 (14%)	196 (38%)	128 (38%)	68 (38%)
None	5 (23%)	96 (19%)	69 (20%)	27 (15%)
0·01–0·04 mV	1 (5%)	33 (6%)	25 (7%)	8 (5%)
0·05–0·09 mV	3 (14%)	56 (11%)	37 (11%)	19 (11%)
0·10–0·19 mV	5 (23%)	60 (12%)	35 (10%)	25 (14%)
0·20–0·50 mV	4 (18%)	52 (10%)	33 (10%)	19 (11%)
>0·50	—	6 (1%)	5 (2%)	1 (1%)
ST-segment code missing	1 (5%)	16 (3%)	6 (2%)	10 (6%)
ST-segment elevation during pain				
No in-hospital pain	3 (14%)	196 (38%)	128 (38%)	68 (38%)
None	6 (27%)	90 (17%)	69 (20%)	21 (12%)
0·01–0·04 mV	5 (23%)	66 (13%)	40 (12%)	26 (15%)
0·05–0·09 mV	3 (14%)	80 (16%)	51 (15%)	29 (16%)
0·10–0·19 mV	4 (18%)	49 (10%)	35 (10%)	14 (8%)
0·20–0·50 mV	—	18 (4%)	9 (3%)	9 (5%)
>0·50 mV	—	1 (0%)	1 (0%)	—
ST-segment code missing	1 (5%)	15 (3%)	5 (1%)	10 (6%)
Comparison of pain ECG with baseline ECG				
Not possible*	6 (27%)	223 (43%)	141 (42%)	82 (46%)
Same ST-segment coding	3 (14%)	82 (16%)	56 (17%)	26 (15%)
More ST-segment depression	10 (45%)	159 (31%)	105 (31%)	54 (31%)
More ST-segment elevation	6 (27%)	101 (20%)	65 (19%)	36 (20%)
Both	3 (14%)	50 (10%)	29 (9%)	21 (12%)

MI, myocardial infarction; ECG, electrocardiogram.
* No pain observed after hospital admission, no (codable) electrocardiogram during pain available, or no (codable) pain free electrocardiogram available for comparison.

Eligibility in HINT not only depended on symptoms and signs at hospital admission but also on history and the patient's reaction to initial management. Furthermore, clinic personnel on routine duty needed to enter patients. Special measures were taken to maintain high quality of operations. Nevertheless, mistakes are unavoidable in a trial like this, and ineligible patients were included. These ineligible patients were excluded from the HINT cohort and hence from the analysis. HINT was designed to answer a therapeutic issue specific to unstable angina as defined. These ineligible patients can not be regarded as having this form of unstable angina. Their inclusion in the analysis would contaminate the findings of those patients that specifically represent the syndrome of unstable angina as defined. It may be argued that patients whose ST-segment or T-wave changes or abnormalities could not be confirmed by the Classification Committee are also ineligible. These patients were nevertheless retained because the treating physician's assessment of electrocardiography needed to prevail.

When the trial started chewing a capsule of nifedipine to relief chest pain was allowed before randomisation. Later it was realized that this might compromise internal validity and the protocol was changed. All enrolments in which nifedipine was used to relieve pain were grouped as improper.

In contrast to ineligible patients, who are known not to have unstable angina, patients with unassessable records were poorly documented so that unstable angina could not be established. They had to be excluded for practical reasons.

It is generally accepted that exclusions based on pre-randomisation data do not compromise internal validity, provided that the exclusion criteria are

Table 3.10 Heart rates and blood pressure at baseline

	Pre-randomisation MI		Previous beta blockade	
	Yes ($N = 22$)	No ($N = 515$)	No ($N = 338$)	Yes ($N = 177$)
Heart rate				
<70 beats min^{-1}	8 (36%)	253 (49%)	136 (40%)	117 (66%)
70–100 beats min^{-1}	13 (59%)	249 (48%)	190 (56%)	59 (33%)
>100 beats min^{-1}	1 (5%)	12 (2%)	11 (3%)	1 (1%)
Missing	—	1 (0%)	1 (0%)	—
Systolic blood pressure				
<126 mmHg	13 (59%)	180 (35%)	113 (33%)	67 (38%)
126–140 mmHg	7 (32%)	172 (33%)	111 (33%)	61 (34%)
>140 mmHg	2 (9%)	160 (31%)	111 (33%)	49 (28%)
Missing	—	3 (1%)	3 (1%)	—
Diastolic blood pressure				
<81 mmHg	12 (54%)	230 (45%)	143 (42%)	87 (49%)
81–90 mmHg	5 (23%)	163 (32%)	105 (31%)	58 (33%)
>90 mmHg	5 (23%)	119 (23%)	87 (26%)	32 (18%)
Missing	—	3 (1%)	3 (1%)	—

MI, myocardial infarction.

absolutely objective and clear[4]. The exclusions from HINT were applied centrally by the Classification Committee, on the basis of pre-randomisation data only, without knowledge of the patient's treatment assignment.

It appeared impossible to obtain reliable data on patients who were diagnosed as unstable angina at admission to hospital but who were not entered. This was due to the temporary nature of the early diagnosis, which generally speaking is not recorded. The problem is exemplified in our own records: the clinical case notes usually made no reference whatsoever to the preceding episode of unstable angina in HINT patients who developed myocardial infarction after randomisation. The absence of these data does not hamper generalization of the HINT findings. The description of the included patients (together with the clinical course of the placebo groups) ultimately determines the clinical spectrum of unstable angina actually studied. Generalization of trial findings is dependent on the characteristics of the patients that were included; it does not pertain to patients that were excluded. By the same token, the total number of enrolments as a percentage of the total number of admissions to the participating coronary care units has nothing to do with the relevance of investigated treatment effects for patients who present with this form of unstable angina.

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4 Treatment, observations, and outcome events

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Design and methods

TRIAL MEDICATION

Patients not on previous maintenance treatment with a beta blocker (for more than three days) were randomly assigned to receive either double placebo, nifedipine six 10 mg doses per 24 hours plus metoprolol placebo, metoprolol two 100 mg doses per 24 hours plus nifedipine placebo, or both drugs. No loading dosages were given. Both nifedipine and metoprolol (or their placebos) were started at the same time. Patients on previous maintenance treatment with a beta blocker were randomly assigned to receive placebo or nifedipine six 10 mg doses per 24 hours, while the previous treatment with a beta blocker was continued; before 13 November 1982 with the same compound and dose as given before, thereafter with two 100 mg doses of metoprolol per 24 hours. Both randomisation procedures were performed for each Clinical Centre separately and in equal proportions.

Unless persistent chest pain developed, the trial medication was continued for at least 48 hours, preferably until angiography was performed or until two days before discharge, so that post-discharge medication could be started in the hospital. In some Clinical Centres trial medication was discontinued after 48 hours in all patients.

An episode of chest pain with pronounced ST-segment or T-wave changes, repeated attacks of chest pain, uncontrollable chest pain, ominous ST-segment or T-wave changes without chest pain, or suspected side-effects warranted discontinuation of trial medication. The decision to reduce or discontinue trial medication was the responsibility of the treating physician. A coding envelope was packed with each package of trial medication so that the true substance of the trial medication could be identified in case of emergencies.

CONCOMITANT TREATMENT

All patients received routine care for at least 48 hours, including electrocardiographic monitoring. Haemodynamic monitoring was instituted if the treating physician thought that it was indicated.

The use of other drugs that may interfere with the evaluation of trial medication effects was restricted: (1) beta blockers other than the ones described above were not allowed; (2) oral long-acting nitrates were continued unchanged if they had been given before admission to hospital—otherwise they were not allowed; (3) neither the prophylactic use of sublingual glyceryl trinitrate, nor a glyceryl trinitrate or a nitroprusside infusion was allowed (transdermal glyceryl trinitrate was not available at that time); (4) calcium antagonists other than the trial medication were not allowed. Other drugs were used as follows: (1) sedatives or anticoagulants according to local practice; (2) antiarrhythmic drugs, digitalis, diuretics, and antihypertensive agents other than beta blockers on indication only.

Chest pain was initially treated as described. If pain persisted further measures were left to the discretion of the treating physician.

DATA COLLECTION AND FOLLOW-UP

All patients were closely followed over the period from hospital admission until 48 hours after randomisation. A detailed scheme of measurements to be obtained and events to be registered was provided. No specific trial observations or measurements were required after 48 hours. Long-term follow-up was continued until at least one year after randomisation.

Twelve-lead electrocardiograms were recorded, in duplicate, every six hours and during and after episodes of chest pain. Blood samples for assays of creatine kinase or its MB-isoenzyme were obtained every six hours until 54 hours after randomisation. (As there is an intrinsic delay in the release of enzymes after the onset of myocardial infarction, enzyme rises between 48 and 54 hours after randomisation were considered consequential to myocardial necrosis that had occurred within 48 hours.) Activities of glutamic oxaloacetic and pyruvic transaminase, lactic acid dehydrogenase, and alpha-hydroxybuteric acid dehydrogenase were determined every 24 hours. Slight deviations of this scheme were allowed. All enzyme determinations were performed locally and subsequently related to local normal values (see chapter 3). Heart rate was recorded every hour. Indirect blood pressures were recorded every

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six hours. Phase V was taken as the diastolic pressure.

A detailed logbook of episodes of chest pain and other medical events was kept. Whenever trial medication was given, this action was recorded on the patient case record form. If trial medication was discontinued, the time of discontinuation and the reason why were recorded, the latter in the following categories: (1) for recurrent chest pain, (2) for side effects, and (3) for other reasons. Incidental departures of the trial medication scheme were noted. Other drugs being taken by the patient were registered as well.

Information on clinical events after 48 hours was collected from clinical records. The time of discontinuation of trial medication (if still applicable), the occurrence of myocardial infarction (serial enzyme values) or death, and medications being taken or prescribed when the patient left hospital were recorded.

Cardiac catheterization and coronary angiography, unless contra-indicated, were performed preferably before discharge but not within 48 hours after randomisation. Information on all angiograms made before January 1985 was collected.

Definition of clinical events

BASIC CONSIDERATIONS

Four (major) clinical events were considered: (1) pre-randomisation myocardial infarction; (2) myocardial infarction within 48 hours; (3) recurrent ischaemia within 48 hours; (4) myocardial infarction within one week. Precise definitions are given below. The Classification Committee reviewed the clinical course of each patient from a standardized report and ascertained which events had occurred. The committee members were neither privy to the patient's trial medication assignment nor to findings at subsequent angiography.

MYOCARDIAL INFARCTION

Myocardial infarction within 48 hours was considered to have occurred if there was a serial enzyme pattern characteristic for acute myocardial infarction with at least one cardiac enzyme significantly raised within 54 hours. Express criteria for 'a typical enzyme pattern' were not defined. Patients who died under the clinical picture of acute myocardial infarction were also classified in this category. The occurrence of myocardial infarction within 48 hours was considered undefined for patients with pre-randomisation myocardial infarction.

For all patients classified as myocardial infarction within 48 hours the Classification Committee determined the most likely time of onset of myocardial infarction retrospectively from the complete clinical history. The decision was based on the temporal relationship between the occurrence of chest pain, changes in the electrocardiogram, and enzyme rises. Onset of myocardial infarction was related to an episode of chest pain. The time of onset was not further specified if the Classification Committee determined that myocardial infarction had started before admission to hospital. The Classification Committee was obliged to choose a time of onset, even if no obvious time of onset was available.

The Classification Committee gave a description of electrocardiographic abnormalities and changes over the period from hospital admission until 48 hours after onset of myocardial infarction for all patients with myocardial infarction. Q-waves, ST-segment displacements, and T-wave inversions were scored at hospital admission, at randomisation, at onset of myocardial infarction. Further, the appearance of new permanent or temporary abnormalities within 48 hours after onset of myocardial infarction was recorded. A Q-wave was scored when greater than 0·03 s. Q-wave equivalents (R-wave greater than 0·03 s in V_1 and R/S ratio greater than 1 in V_2 were scored as inferoposterior Q-waves. ST-segment displacements were scored when at least 0·1 mV. T-wave inversions were scored when at least 0·1 mV. All electrocardiographic abnormalities were scored for three groups of leads: anteroseptal (leads V_1 to V_5, inferior/posterior (leads II, III, and aVF), and lateral (leads I, aVL, and V_6). To complete the electrocardiographic evaluation, the Classification Committee determined the location of the infarction: anteroseptal, infero-posterior, or lateral. The decision depended, in a hierarchy of descending importance, on the location (leads as above) of new Q-waves, of new permanent T-wave inversions, or of ST-segment or T-wave changes at onset.

Myocardial infarction which had occurred in the remainder of the first week after randomisation was ascertained with similar criteria.

RECURRENT ISCHAEMIA WITHIN 48 HOURS

Recurrent ischaemia was considered to have occurred if a chest pain episode with accompanying ST-segment or T-wave changes had taken place. The Classification Committee's decision was taken independently of the treating physician's opinion, which was expressly recorded. The treating physician's judgement on the anginal nature of the chest pain

was accepted at face value. Episodes of chest pain were taken into account irrespective of previous discontinuation of trial medication. Chest pain episodes of which no electrocardiograms were available were ignored. However, if the treating physician had decided to discontinue trial medication for recurrent chest pain and if no electrocardiograms were available, the episode was considered the equivalent of a chest pain episode with ST-segment or T-wave changes.

OUTCOME EVENTS FOR TRIAL MEDICATION EFFECT ASSESSMENT

For the assessment of trial medication effects 'recurrent ischaemia or myocardial infarction within 48 hours' was taken as the main outcome event. Further, 'myocardial infarction within 48 hours', 'myocardial infarction within 48 hours with subsequent Q-wave formation', and 'myocardial infarction within one week' were taken as secondary outcome events.

Results

OCCURRENCE OF MYOCARDIAL INFARCTION

As has been mentioned in chapter 3, 22 of 537 patients (4%) of the HINT cohort had a pre-randomisation myocardial infarction. Of the remaining 515 patients 92 (18%) developed (signs of) acute myocardial infarction within 48 hours after randomisation. Three patients died under the clinical picture of acute myocardial infarction, and significant enzyme rises with a pattern characteristic for acute myocardial infarction occurred in the other 89 patients. In another seven patients significantly raised post-randomisation enzyme values were found, but they were considered to be non-specific: raised activities of glutamic oxaloacetic transaminase in one patient with a known alcohol problem, raised activities of creatine kinase in two patients with a recent intramuscular injection, and four measurement errors. Figure 4.1 shows the presumptive time of onset of acute myocardial infarction in 92 patients with myocardial infarction within 48 hours. In 43 patients (47%) myocardial infarction was thought to have occurred before randomisation despite cardiac enzyme concentrations being below twice the upper limit for normal at that time, in 38 patients (41%) even before admission to hospital. Table 4.1 shows electrocardiographic changes that occurred at the (presumptive) onset of myocardial infarction. No electrocardiographic changes as defined were observed in 19 patients. Figure 4.1 also shows the time

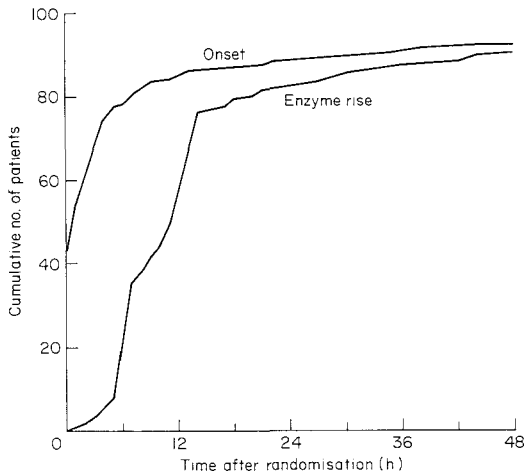

Figure 4.1 Timing of the onset of myocardial infarction and the first significant rise in enzyme concentration for 92 cases of myocardial infarction within 48 hours in 515 patients without enzymatic evidence of infarction at randomisation. The time of the onset of myocardial infarction was determined retrospectively by the Classification Committee from the complete clinical history. The upper line represents the cumulative distribution of the time of onset of myocardial infarction—that is, it represents for each point in time after randomisation the total number of patients with an onset before that time. In 43 cases the onset was judged to have taken place before randomisation; the upper line thus starts at 43. Similarly the lower line represents the cumulative distribution of the time of first rise in enzyme concentration to over twice the local upper limit of normal. No significantly raised enzyme values could be observed in two patients who died soon after onset of myocardial infarction.

Table 4.1 Electrocardiographic changes at the (presumptive) time of onset of myocardial infarction in 92 patients with myocardial infarction within 48 hours

Patients with MI <48 h	92	
Onset before hospital admission	38	
Onset after hospital admission	54	
New Q-waves		7 (13%)*
New ST-segment elevations		21 (39%)*
New ST-segment depressions		24 (44%)*
New T-wave inversions		12 (22%)*
No changes		19 (35%)*

MI, myocardial infarction.
* Numbers in parenthesis indicate percentages of patients with myocardial infarction within 48 hours with an onset after hospital admission.
The time of onset of myocardial infarction was determined retrospectively by the Classification Committee from the complete clinical history.
All patients with pre-randomisation myocardial infarction had an onset before admission to hospital.

Table 4.2 Permanent electrocardiographic abnormalities which developed after onset of myocardial infarction, as registered by the Classification Committee (numbers of patients with percentages in brackets)

	MI_0 ($N = 22$)	MI_{48} ($N = 92$)
New Q-waves	5 (23%)	50* (54%)
New T-wave inversions only	7 (32%)	29 (32%)
Neither of these	10 (45%)	13 (14%)

MI_0, prerandomisation myocardial infarction; MI_{48}, myocardial infarction within 48 hours.
* Includes two cases of fatal Q-wave infarctions not counted in ref. [1].

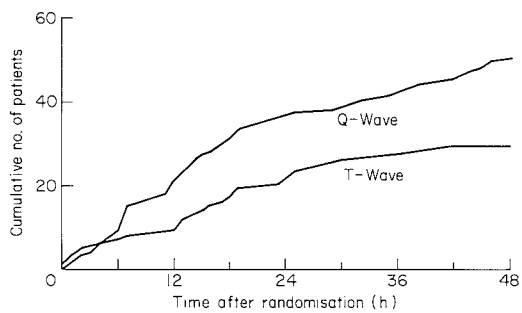

Figure 4.2 Timing of the appearance of new Q waves and of permanent new T-wave inversions for 92 cases of myocardial infarction within 48 hours without enzymatic evidence of infarction at randomisation, as determined by the Classification Committee. The upper line represents the cumulative distribution of the time of appearance of a Q-wave and the lower line that of new permanent T-wave inversion.

of first occurrence of a significant rise in activities of creatine kinase or its MB-isoenzyme. Table 4.2 shows the electrocardiographic changes that occurred after onset of myocardial infarction. New Q-waves developed in 50 of 92 patients (54%) with myocardial infarction within 48 hours. Figure 4.2 shows the time of first appearance of new Q-waves and of new permanent T-wave inversion. Table 4.3 shows the locations of the infarctions. Table 4.4 shows maximum serum activities of creatine kinase, of its MB-isoenzyme, and of glutamic oxaloacetic transaminase over the period from randomisation until 54 hours later. Activities of creatine kinase were recorded in 72 of 89 patients (81%) with non-fatal infarction within 48 hours. Corresponding figures for the MB-isoenzyme of creatine kinase and for glutamic oxaloacetic transaminase were 59 (66%) and 87 (98%). Only a few infarctions were associated with high enzyme releases.

One patient with myocardial infarction within 48 hours died after 48 hours. Of 423 patients without myocardial infarction within 48 hours 20 (5%) developed myocardial infarction in the remainder of the first week after randomisation; four of them died.

RECURRENCE OF CHEST PAIN

Table 4.5 shows recurrence of chest pain within 48 hours for each category of myocardial infarction separately. The episodes of chest pain in patients with pre-randomisation myocardial infarction represented postinfarction angina. The episodes of chest pain in patients with myocardial infarction within 48 hours marked the onset of infarction in most patients but not in all. In 19 of 92 (21%) patients with myocardial infarction within 48 hours no chest pain occurred

Table 4.3 Location of myocardial infarction, as determined by the Classification Committee

	MI_0 ($N = 22$)	MI_{48} ($N = 92$)	Q-wave ($N = 50$)	non-Q-wave ($N = 42$)
Anteroseptal	8 (36%)	38 (41%)	15 (31%)	23 (55%)
Infero-posterior	4 (18%)	36 (39%)	29 (58%)	7 (17%)
Lateral	2 (9%)	15 (16%)	6 (12%)	9 (21%)
Not identifiable	8 (36%)	3 (3%)	—	3 (7%)

MI_0, pre-randomisation myocardial infarction; MI_{48}, myocardial infarction within 48 hours.
Anteroseptal, leads V_1 to V_5; Infero-posterior, leads II, III, aVF; Lateral, leads I, aVL, V_6.

Table 4.4 Maximum activities of creatine kinase, MB-isoenzyme of creatine kinase, and glutamic oxaloacetic transaminase (over the period from randomisation until 54 hours later) in 89 patients with a non-fatal myocardial infarction within 48 hours (numbers of patients with percentages in brackets)

	Cardiac enzymes			
	CK ($N = 72$)	MB-CK ($N = 59$)	GOT ($N = 87$)	MAX ($N = 89$)
<200*	3 (4%)	3 (5%)	34 (39%)	—
200–500	36 (50%)	24 (41%)	39 (45%)	41 (46%)
500–1000	24 (33%)	22 (37%)	10 (11%)	30 (34%)
1000–2000	7 (10%)	7 (12%)	4 (5%)	13 (15%)
>2000	2 (3%)	3 (5%)	—	5 (6%)

CK, creatine kinase; MB-CK, MB-isoenzyme of creatine kinase; GOT, glutamic oxaloacetic transaminase; MAX, maximum of the three activities.
* Maximal activities over 54 hours after randomisation are expressed as percentages of local upper limit for normal.

Table 4.5 Recurrence of chest pain within 48 hours of randomisation (numbers of patients with percentages in brackets)

	MI_0 ($N = 22$)	MI_{48} ($N = 92$)	No MI_{48} ($N = 423$)
None	12 (54%)	19 (21%)	237 (56%)
Without ST-T changes	3 (14%)	5 (5%)	61 (14%)
Without ECG	2 (9%)	6 (7%)	28 (7%)
With ST-T changes	5 (23%)	62 (67%)	97 (23%)

MI_0, pre-randomisation myocardial infarction; MI_{48}, myocardial infarction within 48 hours; ECG, electrocardiogram. Patients to whom more than one category applied were placed in the most severe (i.e. the lower) category.

after randomisation; enzyme rises constitute the only evidence for progression to myocardial infarction. In 97 of 423 patients (23%) without myocardial infarction within 48 hours one or more episodes of recurrent chest pain with accompanying ST-segment or T-wave changes occurred. The Classification Committee decided that recurrent ischaemia had occurred in another two patients because the treating physician had discontinued trial medication for severe chest pain without recording electrocardiograms. Chest pain did not recur in 237 of 423 patients (56%) without myocardial infarction within 48 hours.

BASELINE CHARACTERISTICS IN RELATION TO OUTCOME EVENTS

Table 4.6 shows selected baseline characteristics in relation to the defined outcome events. There were only small differences between the rates of recurrent ischaemia or myocardial infarction within 48 hours of randomisation for respective categories of age, sex, previous myocardial infarction, history of angina, previous beta blockade, and enzyme level. The rates for myocardial infarction within 48 hours varied specifically between patients with a sudden onset of clinical instability (the categories 'no' and 'sudden') on the one hand and those with a more gradual onset of clinical instability (the categories '< 1 month' and 'crescendo') on the other hand. The length of the pain free interval was strongly related to the rate of recurrent ischaemia or myocardial infarction within 48 hours: 62% of patients who had a pain free interval of less than one hour developed recurrent ischaemia or myocardial infarction within 48 as opposed to 22% of those in whom the pain free interval lasted more than three hours. The length of the pain free interval was also strongly related to the other outcome events.

Table 4.7 shows electrocardiographic baseline characteristics derived from the (pain free) electrocardiogram in relation to the defined outcome events. The rate of recurrent ischaemia or myocardial infarction within 48 hours was strongly related to the amount

Table 4.6 Selected demographic and clinical baseline characteristics and corresponding outcome event rates

			Outcome events			
	MI_0	No MI_0	RI/MI_{48}	MI_{48}	MI_{48+Q}	MI_{1w}
Age						
30–54	7	183	69 (38%)	38 (21%)	22 (12%)	45 (25%)
55–61	11	171	56 (33%)	22 (13%)	11 (6%)	26 (15%)
62–70	4	161	66 (41%)	32 (20%)	17 (11%)	41 (25%)
Sex						
Male	20	387	149 (39%)	82 (21%)	48 (12%)	96 (25%)
Female	2	128	42 (33%)	10 (8%)	2 (2%)	16 (13%)
Previous myocardial infarction						
No	14	322	129 (40%)	63 (20%)	38 (12%)	73 (23%)
History only	3	64	25 (39%)	9 (14%)	4 (6%)	13 (20%)
Q-waves	5	129	37 (29%)	20 (16%)	8 (6%)	26 (20%)
History of angina *						
No	8	143	50 (35%)	34 (24%)	18 (13%)	38 (27%)
< 1 month	5	165	66 (40%)	27 (16%)	16 (10%)	32 (19%)
> 1 month, crescendo	5	114	37 (32%)	11 (10%)	4 (4%)	19 (17%)
> 1 month, sudden	4	93	38 (41%)	20 (22%)	12 (13%)	23 (25%)
Previous beta blockade						
No	18	338	121 (36%)	63 (19%)	36 (11%)	74 (22%)
Yes	4	177	70 (40%)	29 (16%)	14 (8%)	38 (21%)
Pain free interval						
< 1 hour	4	133	82 (62%)	45 (34%)	25 (19%)	53 (40%)
1–3 hours	12	186	66 (35%)	31 (17%)	17 (9%)	39 (21%)
> 3 hours	6	196	43 (22%)	16 (8%)	8 (4%)	20 (10%)
Enzyme values at baseline †						
< 100%	—	457	166 (36%)	79 (17%)	44 (10%)	99 (22%)
100–200%	—	58	25 (43%)	13 (22%)	6 (10%)	13 (22%)
> 200%	22	—	—	—	—	—

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{48+Q}, myocardial infarction within 48 hours with subsequent Q-wave formation; MI_{1w}, myocardial infarction within one week.

* Crescendo, angina pectoris of effort present for more than one month with gradual acceleration; sudden, angina pectoris of effort present for at least one month without any acceleration before the presenting episode of angina at rest.

† Maximal values of activities of creatine kinase, MB-isoenzyme of creatine kinase, glutamic oxaloacetic transaminase obtained before randomisation are expressed as percentage of local upper limits for normal.

of ST-segment depression on the (pain free) baseline electrocardiogram. Neither ST-segment elevation nor T-wave inversion on the baseline electrocardiogram related particularly to the defined outcome events. The location of the abnormalities (anterior versus non-anterior) was not predictive of the outcome events.

Table 4.8 shows electrocardiographic baseline characteristics derived from the pain electrocardiogram. One hundred and ninety six patients were entered on the basis of a chest pain episode at home. Among them rates of the defined outcome events were substantially lower relative to those among patients with pain while in hospital. Of 16 patients who suffered chest pain while in hospital the electrocardiogram obtained during pain was either illegible or contained Minnesota incompatibilities rendering the ST-segment undefined. The rate of recurrent ischaemia or myocardial infarction was strongly related to the amount of ST-segment depression on the pain electrocardiogram. On the other hand, ST-segment elevation showed no relation to the rates of the defined outcome events. The comparison of the pain electrocardiogram with the (pain free) baseline

Table 4.7 Baseline characteristics from electrocardiogram with pain absent and corresponding outcome event rates

			Outcome events			
	MI_0	No MI_0	RI/MI_{48}	MI_{48}	MI_{48+Q}	MI_{1w}
ST-segment depression at baseline						
None	7	214	75 (35%)	32 (15%)	18 (8%)	35 (16%)
0·01–0·04 mV	4	69	19 (28%)	10 (14%)	5 (7%)	11 (16%)
0·05–0·09 mV	4	119	42 (35%)	18 (15%)	10 (8%)	23 (19%)
0·10–0·19 mV	1	68	31 (46%)	18 (26%)	12 (18%)	22 (32%)
0·20–0·50 mV	4	25	16 (64%)	8 (32%)	2 (8%)	15 (60%)
ST-code missing	2	20	8 (40%)	6 (30%)	3 (15%)	6 (30%)
ST-segment elevation at baseline						
None	4	100	45 (45%)	22 (22%)	13 (13%)	27 (27%)
0·01–0·04 mV	7	127	45 (35%)	23 (18%)	14 (11%)	28 (22%)
0·05–0·09 mV	4	164	66 (40%)	29 (18%)	17 (10%)	34 (21%)
0·10–0·19 mV	5	91	24 (26%)	11 (12%)	3 (3%)	15 (17%)
0·20–0·50 mV	—	13	3 (23%)	1 (8%)	—	2 (15%)
ST-code missing	2	20	8 (40%)	6 (30%)	3 (15%)	6 (30%)
T-wave inversion at baseline						
Upright	8	145	50 (35%)	26 (18%)	17 (12%)	29 (20%)
0·01–0·09 mV	7	149	60 (40%)	29 (19%)	14 (9%)	33 (22%)
0·10–0·50 mV	7	192	72 (38%)	32 (17%)	17 (9%)	40 (21%)
>0·50 mV	—	24	7 (29%)	3 (13%)	1 (4%)	8 (33%)
T-code missing	—	5	2 (40%)	2 (40%)	1 (20%)	2 (40%)
ST–T abnormalities at baseline*						
None	13	269	98 (36%)	49 (18%)	29 (11%)	55 (20%)
T-wave inversion	2	121	33 (27%)	9 (7%)	4 (3%)	11 (9%)
ST non-anterior	—	18	11 (61%)	7 (39%)	1 (6%)	9 (50%)
ST anterior	5	87	41 (47%)	21 (24%)	13 (15%)	31 (36%)
ST-code missing	2	20	8 (40%)	6 (30%)	3 (15%)	6 (30%)
CIIS-score at baseline						
<9	4	161	58 (36%)	32 (20%)	19 (12%)	34 (21%)
9–20	5	161	63 (39%)	24 (15%)	15 (9%)	29 (18%)
>20	11	172	62 (36%)	30 (17%)	13 (8%)	43 (25%)
Missing	2	21	8 (38%)	6 (29%)	3 (14%)	6 (29%)

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{48+Q}, myocardial infarction within 48 hours with subsequent Q-wave formation; MI_{1w}, myocardial infarction within one week; CIIS, cardiac infarction injury score.

* T-wave inversion, T-wave inversion of at least 0·10 mV; ST non-anterior, ST-segment depression or elevation of at least 0·10 mV in non-anterior leads only; ST anterior, ST-segment depression or elevation of at least 0·10 mV in anterior leads (V_2–V_5).

electrocardiogram was of great importance: event rates markedly depended upon the presence of codable ST-segment changes during pain.

OUTCOME EVENT RATES IN TRIAL MEDICATION GROUPS

Table 4.9 shows the number of pre-randomisation myocardial infarctions per trial medication groups. Also shown are the rates for the defined outcome events for patients without pre-randomisation myocardial infarction. In patients not on previous maintenance treatment with a beta blocker who were treated with nifedipine all four event rates were higher than the corresponding ones for those on placebo. On the other hand, in patients on metoprolol or on the combination, event rates were lower than the rates for those on placebo. There were no appreciable differences between the rates for those on metoprolol and those on the combination. In patients who were on continued maintenance treatment with a beta blocker, the nifedipine group had lower event rates than the placebo group.

Table 4.8 Baseline characteristics from electrocardiogram with pain present and corresponding outcome event rates

			Outcome events			
	MI_0	No MI_0	RI/MI_{48}	MI_{48}	MI_{48+Q}	MI_{1w}
ST-segment depression during pain						
No pain in hospital	3	196	37 (19%)	17 (9%)	8 (4%)	24 (12%)
None	5	96	39 (41%)	13 (14%)	7 (7%)	14 (15%)
0·01–0·04 mV	1	33	13 (39%)	3 (9%)	1 (3%)	5 (15%)
0·05–0·09 mV	3	56	25 (45%)	15 (27%)	11 (20%)	17 (30%)
0·10–0·19 mV	5	60	34 (57%)	18 (30%)	7 (12%)	21 (35%)
0·20–0·50 mV	4	52	33 (63%)	20 (38%)	13 (25%)	24 (46%)
>0·50 mV	—	6	5 (83%)	3 (50%)	1 (17%)	4 (67%)
ST-code missing	1	16	5 (31%)	3 (19%)	2 (13%)	3 (19%)
ST-segment elevation during pain						
No pain in hospital	3	196	37 (19%)	17 (9%)	8 (4%)	24 (12%)
None	6	90	49 (54%)	26 (29%)	16 (18%)	27 (30%)
0·01–0·04 mV	5	66	30 (45%)	11 (17%)	7 (11%)	15 (23%)
0·05–0·09 mV	3	80	37 (46%)	19 (24%)	9 (11%)	23 (29%)
0·10–0·19 mV	4	49	26 (53%)	14 (29%)	8 (16%)	16 (33%)
0·20–0·50 mV	—	18	7 (39%)	2 (11%)	—	4 (22%)
>0·50 mV	—	1	—	—	—	—
ST-code missing	1	15	5 (33%)	3 (20%)	2 (13%)	3 (20%)
Comparison of pain ECG with baseline ECG						
Not possible*	6	223	48 (22%)	24 (11%)	12 (5%)	31 (14%)
Same ST coding	3	82	32 (39%)	11 (13%)	7 (8%)	11 (13%)
More ST-segment depression	10	159	87 (55%)	45 (28%)	25 (16%)	55 (35%)
More ST-segment elevation	6	101	60 (59%)	32 (32%)	18 (18%)	40 (40%)
Both	3	50	36 (72%)	20 (40%)	12 (24%)	25 (50%)

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{48+Q}, myocardial infarction within 48 hours with subsequent Q-wave formation; MI_{1w}, myocardial infarction within one week; ECG, electrocardiogram.
* No pain observed after hospital admission or no (codable) pain free electrocardiogram available for comparison.

Table 4.9 Outcome event rates in trial medication groups

			Outcome events			
	MI_0	No MI_0	RI/MI_{48}	MI_{48}	MI_{48+Q}	MI_{1w}
No previous maintenance treatment with a beta blocker						
Placebo	3	84	31 (37%)	13 (15%)	9 (11%)	14 (17%)
Nifedipine	4	89	42 (47%)	25 (28%)	14 (16%)	28 (31%)
Metoprolol	4	79	22 (28%)	13 (16%)	6 (8%)	15 (19%)
Combination	7	86	26 (30%)	12 (14%)	7 (8%)	17 (20%)
On continued maintenance treatment with a beta blocker						
Placebo	2	81	41 (51%)	16 (20%)	7 (9%)	19 (23%)
Nifedipine	2	96	29 (30%)	13 (14%)	7 (7%)	19 (20%)

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{48+Q}, myocardial infarction within 48 hours with subsequent Q-wave formation; MI_{1w}, myocardial infarction within one week.

Table 4.10 Use of trial medication at randomisation and during follow-up for each trial medication group in 515 patients without pre-randomisation myocardial infarction

	Use in relation to randomisation			
	0	6 h	24 h	48 h
No previous maintenance treatment with a beta blocker				
Placebo	84 (100%)	79 (94%)	72 (86%)	64 (76%)
Nifedipine	89 (100%)	77 (87%)	63 (71%)	56 (63%)
Metoprolol	79 (100%)	78 (99%)	65 (82%)	58 (73%)
Combination	86 (100%)	81 (94%)	69 (80%)	60 (70%)
On continued maintenance treatment with a beta blocker				
Placebo	81 (100%)	72 (89%)	57 (70%)	53 (65%)
Nifedipine	96 (100%)	88 (92%)	77 (80%)	71 (74%)

In almost all patients with pre-randomisation myocardial infarction trial medication was discontinued when the raised enzyme values became known.

Table 4.11 Reasons for discontinuation of trial medication within 48 hours in 515 patients without pre-randomisation myocardial infarction

	No. of patients	No. of patients discontinued	Reason for discontinuation		
			Chest pain	Side-effect	Other
No previous maintenance treatment with a beta blocker					
Placebo	84	20 (24%)	10 (50%)	1 (5%)	9 (45%)
Nifedipine	89	33 (37%)	23 (70%)	2 (6%)	8 (24%)
Metoprolol	79	21 (27%)	9 (43%)	5 (24%)	7 (33%)
Combination	86	26 (30%)	14 (54%)	3 (12%)	9 (35%)
On continued maintenance treatment with a beta blocker					
Placebo	81	28 (35%)	24 (86%)	–	4 (14%)
Nifedipine	96	25 (26%)	14 (56%)	2 (8%)	9 (36%)

THERAPEUTIC INTERVENTIONS

Trial medication was discontinued in almost all patients with pre-randomisation myocardial infarction when raised enzyme values became known. Table 4.10 shows the use of trial medication at randomisation, and 6, 24, and 48 hours after randomisation among 515 patients without pre-randomisation myocardial infarction. At 48 hours the percentage of patients still on trial medication ranged from 63% of patients allocated to nifedipine who were not on previous maintenance treatment with a beta blocker to 76% of patients allocated to placebo who were not on previous beta blockade. Trial medication was discontinued shortly after 48 hours in another 84 patients. After one week only 52 patients were still on trial medication. Table 4.11 shows the reasons for discontinuation of trial medication in 515 patients without pre-randomisation myocardial infarction. The reported side effects for metoprolol or the combination were low heart rates. Most of the discontinuations under the heading 'other' were because of diagnostic findings of myocardial infarction (enzyme rises).

In five patients the randomisation code was broken within 48 hours. One patient developed severe symptoms of flushing which were considered a side effect of nifedipine (the patient was treated with placebo), all other cases in order to determine further treatment after violent chest pain. In another two patients the code was broken after 48 hours because of complica-

tions. The code was broken for 13 patients at discharge from hospital to determine further therapeutic measures.

Previous maintenance treatment with a beta blocker was continued unchanged in 68 of 76 (89%) patients (without pre-randomisation myocardial infarction) admitted to the trial when the protocol required unchanged continuation. Of these 76 patients 26 were on a subtherapeutic dosage, e.g. one 100 mg dose of metoprolol per 24 hours. Previous maintenance treatment with a beta blocker was continued with two 100 mg doses metoprolol in 81 of 101 patients (81%) admitted in the period when the protocol required this. Of these patients 25 were on a subtherapeutic dosage. In the remaining 21 patients previous maintenance treatment with a beta blocker was either continued unchanged or changed to the beta blocker regimen ordinarily used in the pertinent clinic.

Table 4.12 shows the use of drugs other than trial medication before admission to hospital, around randomisation, after randomisation, and at hospital discharge in 515 patients without pre-randomisation myocardial infarction. Oral long-acting nitrates had been given to 100 patients before admission to hospital and were continued in 76 (76%). In 5 of 415 patients not on previous treatment with long-acting oral nitrates, nitrates were started at randomisation. Thus 434 patients did not receive oral long acting nitrates at randomisation. These drugs were later given, on indication, to 46 (11%) of these patients. Oral long acting nitrates were at least once taken after 48 hours by 212 patients. They were prescribed at discharge to 190 (37%) of the 515 randomised patients. (These tallies are shown in the first line of Table 4.12.) Anticoagulants were given to 351 patients (68%), either at randomisation or on indication after randomisation. At randomisation or within 48 hours 14% received diuretics, 3% digitalis and 3% platelet aggregation inhibiting drugs. A continuous glyceryl trinitrate infusion was started, on indication, after randomisation in 13% of the patients.

Chest pain was relieved spontaneously in 16% of 259 patients without pre-randomisation myocardial infarction who experienced chest pain within 48 hours. In 54% of these patients sublingual glyceryl trinitrate sufficed to eliminate chest pain, and in 17% measures like sublingual nifedipine, fentanyl, or an injection with glyceryl trinitrate were taken. In the remaining 13% of patients opiates were needed to control chest pain.

HEART RATE AND BLOOD PRESSURE

Table 4.13 shows heart rate, systolic blood pressure, and diastolic blood pressure over time per trial

Table 4.12 Use of drugs around randomisation, within 48 hours, after 48 hours but before hospital discharge, and at discharge in 515 patients without pre-randomisation myocardial infarction

	At randomisation					Being taken	
	++	+−	−+	−−	Started within 48h	After 48 h	At discharge
Nitrates	76	24	5	410	46	212	190
Anticoagulants	74	2	248	191	29	302	225
Diuretics	50	46	13	406	12	71	74
Cardiac glycosides	12	5	1	497	1	15	13
Antiarrhythmic drugs	2	3	3	507	38	37	29
Other calcium antagonists	—	5	—	510	—	3	3
Nifedipine	—	—	—	515	60	261	247
Glyc trinitrate infusion	—	—	—	515	67	46	15
Positive inotropic drugs	—	—	—	515	10	6	—
Antiplatelet drugs	8	8	—	499	8	23	23
Beta blockers	177	—	—	338	78	410	378

++, the drug was being taken before admission to hospital and was continued at randomisation;
+−, the drug was being taken at admission to hospital but was discontinued at randomisation;
−+, the drug was not being taken before admission to hospital but was started at randomisation;
−−, the drug was not being taken before admission to hospital and was not started at randomisation;
Started within 48 h—an indication to start the drug developed within 48 hours after randomisation;
Being taken after 48 h—the drug was at least once being taken after 48 hours but before hospital discharge;
Being taken at discharge—this drug was being taken (or was prescribed) when the patient left hospital.

Table 4.13 Heart rate (beats min^{-1}), systolic blood pressure (mmHg), and diastolic blood pressure (mmHg) at randomisation, and at hours 6, 24, and 48 per trial medication group

	Time in relation to randomisation			
	0 h	6 h	24 h	48 h
Heart rate (beats min^{-1})				
No previous maintenance treatment with a beta blocker				
Placebo	74	73	73	75
Nifedipine	76	74	75	76
Metoprolol	73	62	61	62
Combination	74	63	64	64
On continued maintenance treatment with a beta blocker				
Placebo	67	63	65	67
Nifedipine	67	67	65	68
Systolic blood pressure (mmHg)				
No previous maintenance treatment with a beta blocker				
Placebo	134	131	128	126
Nifedipine	137	126	124	126
Metoprolol	135	122	119	115
Combination	138	119	117	116
On continued maintenance treatment with a beta blocker				
Placebo	135	129	123	120
Nifidipine	132	118	118	120
Diastolic blood pressure (mmHg)				
No previous maintenance treatment with a beta blocker				
Placebo	86	82	81	80
Nifedipine	84	79	78	79
Metoprolol	86	79	76	75
Combination	86	75	75	74
On continued maintenance treatment with a beta blocker				
Placebo	86	84	79	77
Nifedipine	82	76	74	75

Values are means per trial medication group for patients still on trial medication.

medication group. Measurements at baseline, at hour 6, at hour 24, and at hour 48 are described as means per trial medication group. Measurements as closely as possible to the intended hours were taken. Measurements at hours 6, 24, and 48 needed to be within 2, 4, and 6 hours, respectively, of the intended time. Only measurements taken while the patient still received trial medication are included. Heart rates in patients not on previous maintenance treatment with a beta blocker were lower among patients treated with metoprolol or the combination. There were no appreciable differences in blood pressure either over time or between trial medication groups. A similar picture emerged if measurements obtained after discontinuation of trial medication were included.

ANGIOGRAPHY

An emergency angiography was performed within 48 hours in 29 patients (6%) without pre-randomisation myocardial infarction. An emergency bypass operation was subsequently performed in 2 patients (0·4%). Percutaneous transluminal coronary angioplasty was performed in 2 patients (0·4%). Emergency angiography was performed within 48 hours in two of 22 patients with prerandomisation myocardial infarction; it was followed by a coronary bypass operation in one patient.

Table 4.14 shows the findings of post-randomisation angiography performed within three months of randomisation in relation to the defined outcome events. With the exception of normal findings, which were related to a decreased risk, no relation was found between the extent of coronary atherosclerosis and outcome event rates. The overall picture hardly changed when all angiograms made after randomisation but before January 1985 were taken into account.

Table 4.15 shows findings at angiography within three months of randomisation by trial medication group. Patients on previous maintenance treatment with a beta blocker had more severe coronary atherosclerosis than patients not on previous maintenance treatment with a beta blocker. A detailed report of the angiographic findings will be published separately.

Discussion

Within a week of start of trial medication myocardial infarction had occurred in 25% (22 + 92 + 20 out of 537). Thus there is a considerable risk of myocardial infarction during this period. Similar percentages have been reported before[2]. But the time of onset of infarction (retrospectively determined from the complete clinical history) relative to the time when the diagnosis of suspected angina was made was not given. Figure 4.1 shows that the onset of myocardial infarction was judged to have occurred before the start of trial medication in 43 cases and that there were 34 further cases within six hours of the start trial medication. Only few infarctions occurred later than six hours after the start of trial medication. Thus so far as myocardial infarction occurs in patients diagnosed at hospital admission as having suspected unstable angina, its onset tends to

Table 4.14 Angiographic findings in relation to outcome event rates

			Outcome events			
	MI_0	No MI_0	RI/MI_{48}	MI_{48}	MI_{48+Q}	MI_{1w}
Angiography within three months						
Not performed	11	145	62 (43%)	41 (28%)	24 (17%)	48 (33%)
Normal	—	58	13 (22%)	1 (2%)	—	1 (2%)
1-vessel disease	4	94	39 (41%)	22 (23%)	10 (11%)	26 (28%)
2-vessel disease	2	96	28 (29%)	11 (11%)	8 (8%)	17 (18%)
3-vessel disease	5	108	44 (41%)	15 (14%)	6 (6%)	17 (16%)
Left main disease	—	14	5 (36%)	2 (14%)	2 (14%)	3 (21%)
Angiography before 1 Jan 1985						
Not performed	8	105	46 (44%)	32 (30%)	19 (18%)	37 (35%)
Normal	—	67	13 (19%)	1 (1%)	—	1 (1%)
1-vessel disease	4	100	41 (41%)	23 (23%)	10 (10%)	27 (27%)
2-vessel disease	3	111	36 (32%)	15 (14%)	10 (9%)	23 (21%)
3-vessel disease	7	117	50 (43%)	19 (16%)	9 (8%)	21 (18%)
Left main disease	—	15	5 (33%)	2 (13%)	2 (13%)	3 (20%)

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{48+Q}, myocardial infarction within 48 hours with subsequent Q-wave formation; MI_{1w}, myocardial infarction within one week; normal, no narrowings of at least 50% observed.

Table 4.15 Angiographic findings (obtained within three months of randomisation) in trial medication groups

	No. of patients	No. of patients with cag*	Angiographic findings				
			Normal	1-vessel	2-vessel	3-vessel	Left main
No previous treatment with a beta blocker							
Placebo	84	65	11 (17%)	19 (29%)	19 (29%)	15 (23%)	1 (2%)
Nifedipine	89	67	10 (15%)	22 (33%)	13 (19%)	19 (28%)	3 (4%)
Metoprolol	79	60	13 (22%)	18 (30%)	19 (32%)	9 (15%)	1 (2%)
Combination	86	64	17 (27%)	12 (19%)	11 (17%)	20 (31%)	4 (6%)
On continued maintenance treatment with a beta blocker							
Placebo	81	55	3 (5%)	14 (25%)	13 (24%)	23 (42%)	2 (4%)
Nifedipine	96	59	4 (7%)	9 (15%)	21 36%)	22 (37%)	3 (5%)

*I.e., Coronary angiography within three months of randomisation; normal, no narrowings of at least 50% observed.

cluster around the time of diagnosis. The clinical implications of this finding are considerable and it shows that treatment which aims at the prevention of progression to myocardial infarction will have a limited effect because in most cases it comes too late.

Despite the high frequency of myocardial infarction this trial supports the notion that the prognosis of patients with this type of unstable angina is good. Total one week mortality was only 1·7% (9/537). Our results indicate that the short term risk of recurrent ischaemia or myocardial infarction is primarily related to the interval since the last attack of chest pain on the one hand and to the presence of ST-segment depressions (not to ST-segment elevations!) either on the baseline electrocardiogram or on the pain electrocardiogram and to pain related ST-segment changes on the other. A multivariate analysis of the short term risk in relation to these baseline characteristics is provided in chapter 5.

The data of Table 4.1 indicate that electrocardiograms recorded at onset of infarction were not typical for infarction. This is understandable in view of the fact that evolving infarction was, by definition, missed in these patients. The maximal values for activities of the cardiac enzymes indicate that the infarctions were relatively small.

The presence of pre-randomisation myocardial infarction is a baseline characteristic, which was not known and could not have been known to the treating physician when the patient was entered. The defined outcome events had already occurred before randomisation in these patients, and hence they were not at risk any more for the defined outcome events. For them, relevant outcomes would have been mortality, recurrence of myocardial infarction, enzymatic infarct size, or left ventricular function. However, there are too few of these patients (22) to evaluate efficacy in these terms. Therefore they were excluded from treatment effect assessment (e.g. from Table 4.9). Why were the 43 patients with an onset of infarction before randomisation not excluded as well? In contrast to the former 22 patients, whose diagnosis was based on pre-randomisation enzyme values only, the latter could only be identified on the basis of enzyme values obtained after randomisation. Using these as a basis for exclusion could compromise internal validity, for instance if any of the trial medications affects the release of enzymes from the necrotic myocardium rather than the amount of necrosis.

The aims of early pharmacologic treatment in patients identified at hospital admission as having suspected unstable angina is the prevention of recurrent ischaemia or progression to myocardial infarction. Treatment has failed if either of these untoward events occurs. For this reason, recurrent ischaemia or myocardial infarction (i.e. failure of treatment) was chosen as the main outcome event to evaluate treatment effects. The other outcome events (myocardial infarction within 48 hours, idem with subsequent Q-wave formation, myocardial infarction within one week) also represent failure of treatment but of a more severe kind. To take recurrence of ischaemia alone as outcome event would be meaningless because one would implicitly assume that patients who progress to myocardial infarction without renewed chest pain are successfully treated.

The independent review by the Classification Committee was undertaken to strengthen the methodology of the trial by applying uniform reproducable standards in the ascertainment of the (subjective) outcome events. All episodes of chest pain and enzyme values were taken into account, irrespective of previous discontinuation of trial medication or any departure from the trial protocol. The tallies of outcome events per trial medication group (Table 4.9) were thus drafted in strict accordance with the intention-to-treat principle[3]. The intention-to-treat principle follows naturally from the nature of the clinical problem: how useful is initiation of early treatment with nifedipine or metoprolol in patients presenting with symptoms and signs of suspected unstable angina.

Maintenance of the highest possible degree of blindness was seen to be particularly important in the context of HINT. Nonspecific measures may have a substantial impact on recurrence of chest pain or at least on the patient's perception of it. Clinic personnel and Coordinating Centre staff were responsible for the acquisition and processing of information on outcome events (e.g. recording electrocardiograms and obtaining blood samples for enzyme measurements). Blinding of the Classification Committee was extremely important because their decisions were to a certain extent subjective, e.g. with regard to the presence of ST-segment or T-wave changes during pain. We believe that the procedure as a whole was such that outcome events were ascertained without knowledge of the patient's treatment assignment. It has been argued that the chronotropic effect of beta blockers precludes the maintenance of blindness in trials of beta blockers versus non-beta blocking treatments. We also observed that the mean heart rates in the beta blocker and the combination groups were lower than in the corresponding placebo and nifedipine groups. However, the variability in heart rate was, as expected, sufficiently large to cause a considerable overlap between the groups. For this reason, there is sufficient uncertainty in the prediction of the trial medication assignment in an individual patient.

The angiographic findings as presented in Tables 4.14 and 4.15 are difficult to interpret. To begin with, they reflect the degree of coronary atherosclerosis that was present weeks after randomisation in those patients in whom angiography was performed (72%). Hence they do not represent a baseline characteristic in the strict sense. Further, angiography is generally carried out after stabilization of symptoms (i.e. a few days after hospital admission at the earliest), unless there are compelling reasons for an emergency procedure, e.g. symptoms that are refractory to maximal pharmacologic treatment. Thus in most patients angiographic findings are not relevant to the initial management.

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5 Data analysis

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Introduction to data analysis

The methodology and findings of HINT have been described in chapters 3 and 4. Together, these chapters document the experience of 668 patients admitted to hospital for unstable angina between 1981 and 1984. This experience, however, does not represent the ultimate result of HINT. The objective of HINT was to learn about the therapeutic benefit of nifedipine, metoprolol, and their combination in their capacity to prevent recurrent ischaemia or myocardial infarction in suspected unstable angina. More specifically, the objective was to obtain estimates of the magnitudes of the treatment effects. The eventual result of HINT would then be a view (an opinion) about these treatment effects. This view will not be based on the HINT findings alone—it will also depend on findings of other trials, on pathophysiological and pharmacologic insights, and on other clinical observations. The principle is that prior views are updated in the light of new findings, in this case from HINT. The extent to which the prior views are updated may be regarded as the inference drawn from the trial.

Even after results from a particular trial become available, the opinions of experts usually remain quite diverse and, hence, subjective. The reasons for this are two-fold: (1) the views formulated before disclosure of the results are subjective; and (2) the evidence itself from a clinical trial is subject to interpretative differences, in particular as to which indication findings may be applied. It is thus evident that the purpose of data analysis cannot be taken as that of reaching a conclusion about the investigated treatment effects. Its purpose is to summarize the evidence in the data with respect to these effects. In the end, conclusions will be drawn by the reader of the study report.

The summarization of evidence rests on three elements: (1) a description of the study design—to allow a judgement of internal validity; (2) a summary presentation of the observations themselves; and (3) estimates of the treatment effects together with an indication of their precision. Each of these elements is discussed below.

The description of the study design allows the reader to form an opinion about internal validity. If methodology is seriously flawed, the evidence is invalid and no inference whatsoever can be drawn. The presentation of methodology is usually not considered a part of data analysis per se. HINT methodology was presented in chapters 3 and 4. Its actual implementation in the Clinical Centres, which also pertains to validity, is presented in chapter 6.

The raw observations (the data) contain the information on the treatment effects under study. They need be summarized in concise form, which usually consists of tabulations of the observations according to key design factors. This process is generally referred to as data reduction. Its purpose is to ensure that the reader acquires some familiarity with the data. It also includes the baseline profile of the patients admitted to the trial, which defines the clinical spectrum of the disease entity actually studied. Reduced data of HINT were presented in chapters 3 and 4.

The primary objective of data analysis is the generation of valid estimates of the treatment effect(s) in combination with an appropriate indication of its precision (a confidence interval). Secondary objectives are the identification of baseline characteristics that are important determinants of the course of the illness (prognosis) and the identification of baseline characteristics that specifically modify treatment effects (effect modification or subgroup analysis). The derivation of effect estimates, the assessment of prognosis, and the study of effect modification are generally referred to as data analysis (in its usual sense), which in reference to HINT is the subject of this chapter.

Two approaches to effect estimation are presented. The first approach, generally referred to as simple analysis, is based on a simple, direct comparison of outcomes between treatment groups without taking account of baseline characteristics; it leads to crude (i.e. unstratified) effect estimates. In the second approach, commonly known as stratified analysis, the investigator also evaluates the role of baseline characteristics using appropriate stratification (or multivariate methods). The effect estimates that result from it have been adjusted for known imbalances in baseline composition of the treatment groups. Although we regard stratified analysis primary, a detailed presentation of simple analysis

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seems warranted. Firstly, an understanding of this procedure is necessary before the general principles of stratified analysis can be appreciated. Secondly, a simple analysis is usually performed even if the role of baseline characteristics is further explored.

The conventional approach to data analysis in clinical trials is that of statistical hypothesis testing. Application of this method in clinical trial data analysis is, in our view, based on an improper perception of the objectives of a clinical trial. The purpose of carrying out a clinical trial is to determine the magnitude of the therapeutic benefit of the index treatment relative to the reference treatment, and not to establish whether any therapeutic benefit exists. As a consequence, we have refrained from presenting *P*-values or any other quantity associated with statistical hypothesis testing.

Simple analysis

MEASURES OF OUTCOME EVENT FREQUENCY

Table 5.1 shows the general data lay-out for simple analysis. Outcome event occurrence at the group level is measured as a rate defined as the proportion of patients that develops the outcome event during the follow-up period: the index rate r_1 equals a/n_1, and the reference rate r_0 equals b/n_0. A rate of this type is a dimensionless quantity; its value must range between zero and one. Its interpretation specifically relates to the time period to which it applies: it measures the (average) risk (or probability) of an individual patient developing the outcome event within the follow-up period when (initially) exposed to either index or reference treatment.

Table 5.1 Data lay-out for simple analysis

	Outcome event			
Treatment	Yes	No	Total	Rate
Index	a	c	n_1	$r_1 = a/n_1$
Reference	b	d	n_0	$r_0 = b/n_0$

POINT ESTIMATION OF TREATMENT EFFECTS

A measure of treatment effect reflects the magnitude of the therapeutic benefit of the index treatment relative to the reference treatment with regard to the outcome of interest. In principle, it involves a direct comparison of frequency measures for different treatment groups. A ratio comparison of two rates is called a rate ratio (RR), which may be computed directly from the ratio of two rates as follows:

$$RR = \frac{r_1}{r_0} = \frac{a}{n_1} \Big/ \frac{b}{n_0},$$

where r_1 and r_0 are the observed rates for the index and reference group respectively. An alternative would be a difference comparison of two rates: the rate difference (RD), which may be computed from the difference of two rates as follows:

$$RD = r_1 - r_0 = \frac{a}{n_1} - \frac{b}{n_0}.$$

The rate ratio provides a relative measure of the two rates while the rate difference provides an absolute comparison. The rate ratio is more commonly used, because it gives the most intuitive comparison. In what follows the rate ratio is taken as the treatment effect measure of interest. It represents a point estimate of the true risk ratio, i.e. the ratio of the risk for developing the outcome event under index treatment to that under reference treatment. A rate ratio of unity points towards equivalence of risk under the two (compared) treatments. A rate ratio greater than unity indicates that the risk for the outcome event under index treatment may exceed that under reference treatment (i.e. a deleterious effect of index treatment relative to the reference treatment). A rate ratio less than unity indicates that the index treatment may reduce the risk for the outcome event relative to the reference treatment (i.e. therapeutic benefit of the index treatment relative to the reference treatment).

INTERVAL ESTIMATION OF TREATMENT EFFECTS

The observed rates r_1 and r_0, and thus the observed rate ratio, are subject to random variation: other values of the rates and of the rate ratio are expected if the trial were replicated. Hence, the observed rate ratio randomly deviates from the true risk ratio, i.e. from the true treatment effect the investigator intends to measure. (The concept of precision as outlined in chapter 2 thus concerns random variation in the rate ratio.) It is essential that the point estimate is supplemented with some measure of the random variation. Only then, the reader can fully appreciate the information on the magnitude of the treatment effect that is provided by the data.

One approach is to use the confidence interval, which consists of a range of values (surrounding the point estimate) of the true treatment effect consistent with the observed data. Values close to the point estimate are most consistent with the data, whereas those at the outer sides show only marginal consis-

tency. The confidence interval may be considered as an interval estimate of the treatment effect. Its width is determined by the size of the treatment groups and by a chosen value that specifies the degree of consistency between the limits of the interval and the data. This so-called confidence level, arbitrarily but conventionally set at 95%, gives the confidence interval sufficient width so that it contains the true treatment effect (risk ratio) in 95% of the applications. This frequency behaviour has led to the notion that one may be 95% confident that the 95%-confidence interval will contain the true risk ratio. This does not imply that one may indeed be 95% confident that an actually calculated 95%-confidence interval contains the true risk ratio (even in the absence of biases). Such confidence seems only warranted when no other information on the risk ratio is available. The 95%-confidence interval is nothing more than a statistic to quantify the precision of the effect estimate. Its width primarily depends on the size of the treatment groups: the larger the treatment groups are, the narrower the confidence interval. Small studies have wide confidence intervals—they convey little information; large studies have narrow confidence intervals—they convey a large amount of information. The confidence interval may be viewed to represent the stability of the measurement: a short interval (in a large study) indicates that values close to the one actually observed are expected if the study were replicated; a wide interval (in a small study) indicates that repeat studies may produce rate ratios that are vastly different. The confidence interval accounts the effect of random variation only; it does not pertain to any form of systematic error that is due a deficiency in design, conduct, or analysis of the study. Methods to calculate confidence intervals for rate ratios are provided in appendix II on page 67.

CRUDE EFFECT ESTIMATION IN HINT

Table 5.2 shows crude rate ratios with 95%-confidence intervals for comparisons of trial medications relative to placebo with regard to three of the four defined outcome events. Because the overall occurrence of the outcome event 'myocardial infarction within 48 hours with subsequent Q-wave formation' was rather low, effect estimates are not provided for this outcome event.

Stratified analysis

Valid measurement of the therapeutic benefit of one treatment relative to another is only possible with groups that could be expected to produce identical outcomes in the absence of a differential therapeutic effect. A balanced distribution of the risk (or propensity) for developing the outcome event is a prerequisite for valid comparison. The purpose of randomisation is to achieve identity of distribution in baseline risk between the treatment groups. As the randomisation procedure itself is subject to chance variation, distributions are only identical on the long run. Randomisation does not guarantee identity of risk distributions in a given trial. A minor and sometimes even a major imbalance in baseline risk may arise by chance alone. If this occurs, the crude rate ratio gives a distorted impression of the true treatment effect. The validity of the effect estimates ultimately depends on the extent to which the random assignment procedure has accomplished identity of distribution for baseline risk.

Table 5.2 Crude rate ratios (with 95%-confidence intervals in brackets) for comparisons of index trial medications with placebo

	RI/MI_{48}	MI_{48}	MI_{1w}
No previous maintenance treatment with a beta blocker			
Nifedipine/placebo	1·28 (0·90, 1·84)	1·82 (1·01, 3·31)	1·89 (1·08, 3·34)
Metoprolol/placebo	0·75 (0·48, 1·18)	1·06 (0·53, 2·13)	1·14 (0·59, 2·19)
Combination/placebo	0·82 (0·53, 1·25)	0·90 (0·44, 1·84)	1·19 (0·63, 2·24)
On continued maintenance treatment with a beta blocker			
Nifedipine/placebo	0·60 (0·41, 0·86)	0·69 (0·35, 1·33)	0·84 (0·48, 1·48)

RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{1w}, myocardial infarction within one week. Crude rate ratios may be considered treatment effect estimates without taking account of baseline characteristics.

The fact that randomisation is unreliable in producing treatment groups with comparable baseline risk is a major concern in data analysis. As baseline risk is an abstract and hence immeasurable notion, its evaluation is achieved by a careful analysis of (measurable) baseline characteristics that bear on prognosis. Stratified analysis and multivariate analysis are two data analytic tools that provide a means of obtaining undistorted effect estimates when the data indicate that influential baseline characteristics are differentially distributed. In stratified analysis distortion is avoided by evaluating treatment effects within strata defined by one or more baseline characteristics. The results of the stratum specific comparisons are combined into one single overall estimate. The resulting effect estimate has been adjusted for imbalances of the involved baseline characteristics. Multivariate analysis involves the construction of a model to describe simultaneously the functional relationship between the outcome on the one hand, and treatments and baseline characteristics on the other. The model allows to obtain effect estimates that have been adjusted for the joint imbalance of all baseline characteristics entered into the model.

Table 5.3 Summary information for stratified analysis involving the pain free interval. The information refers to the comparison of nifedipine with placebo for recurrent ischaemia or myocardial infarction within 48 hours among patients not on previous maintenance treatment with a beta blocker

	Placebo	Nifedipine	Weight
All patients	37% (31/84)	47% (42/89)	
Pain free interval			
< 1 hour	63% (12/19)	72% (21/29)	0·26
1–3 hours	39% (9/23)	44% (14/32)	0·36
> 3 hours	24% (10/42)	25% (7/28)	0·38
Standardized rate	39·7%	44·2%	
Rate ratio			
adjusted via standardization		1·11	
adjusted via M–N method		1·11 (0·80, 1·59)	
crude		1·28 (0·90, 1·84)	

M–N, Miettinen–Nurminen (see text).
Percentages are observed rates of recurrent ischaemia myocardial infarction within 48 hours, with tallies in brackets. Weights were taken proportional to overall stratum size among patients not on previous maintenance treatment with a beta blocker. The standardized rate ratio was obtained as the ratio of the standardized rates. Intervals in brackets indicate 95%-confidence intervals.

STRATIFIED ANALYSIS INVOLVING ONE BASELINE CHARACTERISTIC

The general principles of stratified analysis are now illustrated in an example from HINT, in which the pain free interval is involved in the comparison of nifedipine with placebo among patients without previous maintenance treatment with a beta blocker. The resulting treatment effect estimate is adjusted for baseline incomparability of the pain free interval. This example is presented to ensure that the reader obtains an understanding of adjustment by stratified analysis. Note that the ultimate goal is to adjust for incomparability of overall baseline risk, and not for incomparability of one baseline characteristic.

The pain free interval is a strong indicator of risk (see Table 4.6). Table 5.3 provides the required information for stratified analysis. To begin with, rates and tallies for recurrent ischaemia or myocardial infarction within 48 hours are presented, both overall and according to categories defined by the pain free interval. From the denominators of the stratum-specific rates we read that of 89 patients allocated to nifedipine 29 (33%) had a pain free interval of less than one hour, in contrast to only 19 of 84 patients (23%) allocated to placebo. As this distribution indicates that the nifedipine group has a higher risk for developing recurrent ischaemia or myocardial infarction within 48 hours, it seems natural to inquire as to how much of the apparent (negative) effect of nifedipine might be ascribed to it.

The basic technique is standardization of rates. For each trial medication group an overall standardized rate was obtained as a weighted average of stratum-specific rates. To do so, we first assigned weights to the strata, in this case proportional to the size of the overall stratum (i.e. according to the percentages in third column of the upper panel in Table 3.7). The standardized rates were 39·7% for placebo and 44·2% for nifedipine. These rates may be interpreted as those that would have been obtained had randomisation produced a perfect balance for the pain free interval. An adjusted rate ratio is obtained as the ratio of the two standardized rates. Note that the standardized rate ratio has become independent of the actual distribution of the pain free interval. The weights as chosen above, while intuitively attractive, are not optimal on precision grounds. Weights proposed by Miettinen and Nurminen are preferable because they yield (marginally) shorter confidence intervals[1]. (The involved calculations, however, are complex.) The resulting point estimates with their 95%-confidence intervals are also presented in Table 5.3. Crude rate ratios are provided for comparison. Other methods for combining the information over

the strata are available. A statistical discussion of these methods is provided in appendix II on page 67.

The distortion in the crude effect estimate that may be attributed to the unbalanced distribution of the pain free interval emanates from the comparison of the adjusted rate ratio (1·11) with the crude rate ratio (1·28). This comparison reveals the magnitude of the distortion, which the investigator then must take into account in reporting of the results. In general, the magnitude of the distortion depends on the degree of imbalance but also on the strength of the relationship between the baseline characteristic and the outcome: a slightly uneven distribution of a very influential baseline characteristic may cause a greater distortion than a substantial imbalance of a marginally influential baseline characteristic. Any assessment of baseline comparability that fails to appreciate both aspects is inappropriate.

The above example illustrates a concept which is known in nonexperimental epidemiology as confounding, which is said to be present if there is an appreciable difference between the crude and adjusted effect estimate. Confounding in the context of clinical trials is a chance phenomenon: it results from a randomly arisen imbalance in baseline composition of the treatment groups. Confounding in (or distortion of) the crude effect estimate is removed by appropriate stratification.

From the stratum-specific rates in Table 5.3, one may obtain stratum-specific rate ratios: 1·14, 1·13, and 1·04 for the respective categories of the pain free interval. The similarity of these stratum-specific rate ratios indicates that treatment effects (expressed as rate ratios) are essentially equal within each of the three strata. The inspection of stratum-specific rate ratios for changes in the magnitude of the treatment effect according to categories defined by a baseline characteristic is referred to as the study of effect modification or as subgroup analysis. The study of effect modification and the removal of confounding are related but different issues, both requiring the division of data into strata. The observation of uniform treatment effect in the strata in the above example reflects a natural phenomenon outside the study: the absence of a differential treatment effect according to the length of the time interval between the last attack of chest pain and initiation of treatment. By contrast, the presence of confounding is due to the fact that a baseline characteristic appeared unevenly distributed and is, hence, a randomly arisen nuisance.

We now continue with the assessment of baseline risk. Evaluation and description of effect modification is provided thereafter.

Overall baseline risk

In most instances not one but several influential baseline characteristics require simultaneous assessment: imbalances in two baseline characteristics may either mitigate or amplify one another, or marginal imbalances in many characteristics may amount to substantial distortion. Failure to consider combined effects of all influential baseline characteristics may lead to effect estimates that are still distorted. Stratified analysis involving several baseline characteristic is a direct approach but can only be applied with a few baseline characteristics because the number of patients per stratum rapidly decreases with an increasing number of baseline characteristics.

The goal of randomisation is to achieve identity of distribution of overall baseline risk. What is needed in the evaluation of baseline comparability, is some indication of risk in individual patients, one single score that pulls together the influence exercised on the outcome by the various baseline characteristics, which may act as a proxy for overall baseline risk. Stratified analysis involving that score would eliminate all distortion that can knowingly be attributed to imbalance of baseline risk. This principle was introduced to nonexperimental epidemiology in 1976 by Miettinen, where it is known as confounder summarization[2]. It capitalizes on the principle that baseline comparability ultimately hinges on a composite but univariate dimension: baseline risk.

Multivariate logistic regression analysis can be used to provide that summary score. Logistic regression quantifies the joint functional relationship between individual baseline characteristics and (aggregate) baseline risk. Logistic in this context means that a mathematical function known as the logistic function is employed to describe the relationship between baseline characteristics on the one hand and the probability of developing the outcome event (i.e. risk) on the other. The choice of which baseline characteristics to include in the model is in the hands of the investigator; decisions are usually taken on grounds of goodness of fit and medical plausibility. The influence exercised by the individual baseline characteristics is expressed in weights (regression coefficients), which can be estimated from the data. The use of this model also implies uncertainties about the appropriateness of the logistic function to describe the functional relationship between baseline characteristics and risk.

Once the model has been fitted to the data, the estimated baseline risk can be calculated for each individual patient from the weights and the respective values of the baseline characteristics. The next step

involves the forming of strata representing different levels of baseline risk, which then may be used in stratified analysis. Note that estimation of baseline risk includes multivariate analysis of the risk profile, which is a companion objective of data analysis.

Multivariate logistic modelling is necessarily somewhat technical. Basic properties of the logistic model and the actual fitting of the logistic model to the HINT data are described in appendix I (page 65). The risk profile of HINT patients is further explored below. Stratified analysis involving the grouping of patients in categories of baseline risk is provided thereafter.

DETERMINANTS OF RISK IN HINT PATIENTS

The baseline risk for recurrent ischaemia or myocardial infarction within 48 hours is defined as the probability that recurrent ischaemia or myocardial infarction would occur given the patient's baseline characteristics and trial medication assignment to placebo. It is noted that the modelling procedure permits to estimate risk under placebo irrespective of the patient's actual trial medication assignment. The objective was to find the combination of variables that mose closely predicted recurrence of ischaemia or occurrence of myocardial infarction within 48 hours. Baseline characteristics were selected for inclusion in the model on the basis of their overall (statistical) contribution to prediction and on medical plausibility.

None of the characteristics related to the patient's history or medication before admission to hospital was selected. Previous maintenance treatment with a beta blocker was kept in the model, although it did not meet the statistical criterion. Only the interval since the last attack of chest pain and certain electrocardiographic characteristics (the presence of at least 0·1 mV ST-segment depression on the baseline electrocardiogram, the absence of a pain electrocardiogram, the presence of more ST-segment or more ST-segment elevation during pain than at baseline) were sufficiently predictive for recurrent ischaemia or myocardial infarction with 48 hours to be included in the model.

Based on the logistic function, estimated baseline risk was calculated for each of the 515 patients without pre-randomisation myocardial infarction. Patients were ranked accordingly and subsequently divided into three strata of low, medium, and high baseline risk. The boundaries were chosen so that each stratum contained an equal number of patients in whom recurrent ischaemia or myocardial infarction had occurred. The estimated baseline risk and the corresponding grouping are (newly constructed) baseline characteristics. Table 5.4 shows the distribution of the estimated baseline risk. Of 515 patients 59% was grouped as 'low', 24% as 'medium' and 17% as 'high' risk. Also shown are rates of the defined outcome events per stratum of baseline risk. The observed rates for recurrent ischaemia or myocardial infarction with 48 hours were 21%, 53%, and 69%. These rates indicate that the strata are, indeed, associated with substantially different risk levels.

Table 5.5 shows estimated baseline risk for a host of different profiles in baseline composition. By way of illustration, a patient without previous maintenance treatment with a beta blocker, randomised within one hour after relief of chest pain, with 0·2 mV ST-segment depression during pain, which was attenuated to 0·1 mV after relief of chest pain, had an estimated baseline risk of 78% (sixth line, left percentage in Table 5.5), whereas a patient without previous maintenance treatment with a beta blocker, randomised within six hours of spontaneous relief of chest pain at home with only T-wave inversions on the baseline electrocardiogram has a baseline risk of only 15% (first line, right percentage in Table 5.5).

These results indicate that the short-term risk of recurrent ischaemia or myocardial infarction is primarily related to the interval since the last attack of pain on the one hand and to the presence of resting ST-segment abnormalities and pain related ST-segment changes on the other. These associations are also medically plausible because by definition the condition of patients with a long interval between last pain attack and diagnosis has stabilized; the second finding accords with current views and previous findings on the relevance of electrocardiography in such patients[3–5]. These associations also emerged from univariate analysis (see Tables 4.6, 4.7, and 4.8). The multivariate analysis, however, placed the contributions of each of the individual baseline characteristics in proper perspective. A comparison of the upper panel of Table 5.5 with the lower panel indicates that patients on previous maintenance treatment with a beta blocker have a higher (innate) risk for developing recurrent ischaemia or myocardial infarction, conditional on the presence of other determinants of risk.

Stratified analysis in HINT involving baseline risk

The estimated baseline risk is now considered the only factor requiring control in stratified analysis. Stratified analysis thus proceeds as before, but now with the grouping according to estimated baseline risk. Before passing to this, we first provide informa-

Table 5.4 Grouping according to estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours and corresponding outcome event rates

	MI_0 ($N = 22$)	no MI_0 ($N = 515$	Outcome events			
			RI/MI_{48}	MI_{48}	MI_{48+Q}	MI_{1w}
Baseline risk						
Low	13	303	65 (21%)	28 (9%)	13 (4%)	35 (12%)
Medium	5	126	67 (53%)	28 (22%)	17 (13%)	32 (25%)
High	4	86	59 (69%)	36 (42%)	20 (23%)	45 (52%)

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{48+Q}, myocardial infarction within 48 hours with subsequent Q-wave formation; MI_{1w}, myocardial infarction within one week.
The boundaries for the risk strata were 44% and 64%.

tion on the actual composition of the trial medication groups. Table 5.6 shows the distributions between the trial medication groups of those baseline characteristics that were retained in the logistic model. Distributions of other baseline characteristics are irrelevant—for their control does not alter trial medication effect estimates. Table 5.6 also shows the distribution of the grouping for baseline risk for recurrent ischaemia or myocardial infarction within 48 hours; it was distributed differently over the trial medication groups: among patients not on previous maintenance treatment with a beta blocker 18% of those assigned to nifedipine were high risk; for the other three trial medication groups this percentage ranged from 5% to 12%. The higher risk of the nifedipine group was primarily due to a relatively large proportion (33%) of patients in whom trial medication was started within one hour after the last attack of chest pain (the strongest determinant of risk, Table 5.5). In patients who were on continued beta blockade the same applied to patients assigned to placebo, although to a lesser extent.

Table 5.7 shows estimates of the effects that have been adjusted for unbalanced distributions of (estimated) baseline risk together with their 95%-confidence intervals for all choices of index trial medication relative to placebo.

(Table 5.8a and 5.8b provide detailed information on how these adjusted estimates were obtained in stratified analysis involving estimated baseline risk. Shown are rates for the three outcome events at issue, both overall and according to stratum of (estimated) baseline risk for recurrent ischaemia or myocardial infarction. Also shown are standardized overall rates for each trial medication group (obtained as weighted averages of stratum-specific rates with weights proportional to the size of the overall risk stratum), adjusted rate ratios and their 95% confidence intervals. Crude rate ratios together with their 95%-confidence intervals are provided for comparison.)

As could have been expected, adjustment for estimated baseline risk hardly affected the effect estimates for metoprolol or the combination among patients not on previous maintenance treatment with a beta blocker. By contrast, adjustment attenuated the salutary effect of nifedipine among patients on previous maintenance treatment with a beta blocker and the negative effect of nifedipine among patients not on previous maintenance treatment with a beta blocker as well. The width of the confidence intervals for 'myocardial infarction within 48 hours' indicates that the amount of information for this outcome event is only marginal. The amount of information with respect to the other outcome events is respectable, although not overwhelming.

Effect modification

The study of effect modification is aimed at elucidating differences in therapeutic benefit between subgroups of patients defined by different categories of one or more baseline characteristics. Three sources of difficulty usually hinder the study of effect modification in clinical trials. Firstly, the study size is usually marginal with respect to the main comparison, which precludes a sufficiently precise assessment of effect modification. Secondly, the investigator may elect to examine effect modifying properties of a host of baseline characteristics and to report those that are evident upon inspection. Thirdly, effect modification

Table 5.5 Estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours (with corresponding risk stratum) for different baseline profiles

	Pain free interval (hours)		
	<1	1–3	>3
No previous maintenance treatment with a beta blocker			
No pain in hospital			
No ST depression at baseline	38% (l)	21% (l)	15% (l)
ST depression at baseline	56% (m)	36% (l)	27% (l)
Pain ECG present, same ST coding*			
No ST depression at baseline	49% (m)	30% (l)	22% (l)
ST depression at baseline	67% (h)	47% (m)	37% (l)
Pain ECG present, more ST depression*			
No ST depression at baseline	63% (m)	43% (l)	33% (l)
ST depression at baseline	78% (h)	61% (m)	50% (m)
Pain ECG present, more ST elevation*			
No ST depression at baseline	67% (h)	47% (m)	37% (l)
ST depression at baseline	81% (h)	65% (h)	55% (m)
Pain ECG present, both*			
No ST depression at baseline	78% (h)	61% (m)	51% (m)
ST depression at baseline	88% (h)	76% (h)	68% (h)
On continued maintenance treatment with a beta blocker			
No pain in hospital			
No ST depression at baseline	48% (m)	29% (l)	21% (l)
ST depression at baseline	65% (h)	45% (m)	36% (l)
Pain ECG present, same ST coding*			
No ST depression at baseline	59% (m)	39% (l)	30% (l)
ST depression at baseline	75% (h)	57% (m)	47% (m)
Pain ECG present, more ST depression*			
No ST depression at baseline	72% (h)	53% (m)	43% (l)
ST depression at baseline	84% (h)	70% (h)	60% (m)
Pain ECG present, more ST elevation*			
No ST depression at baseline	75% (h)	57% (m)	47% (m)
ST depression at baseline	86% (h)	73% (h)	64% (h)
Pain ECG present, both*			
No ST depression at baseline	84% (h)	70% (h)	61% (m)
ST depression at baseline	92% (h)	83% (h)	76% (h)

ST depression at baseline, ST-segment depression of at least 0·1 mV on the baseline electrocardiogram; (h), high risk; (m) medium risk; (l), low risk; ECG, electrocardiogram.
Percentages are estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours, with corresponding risk stratum in brackets.
* From the comparison of the pain electrocardiogram with the baseline electrocardiogram; both more ST-segment depression in some leads and more ST-segment elevation in other leads.
The boundaries for the risk strata were chosen as 44% and 64%.

may be dependent upon the choice of the effect measure, e.g. what appears to be a nonuniform effect on a rate ratio scale may seem more or less uniform on a rate difference scale. Consequently, results of data analysis undertaken to evaluate effect modification should be approached with caution. The investigator's judgment about effect modification, and the reader's judgment as well, should not be restricted to the appearance of the data at hand; when it is available, outside knowledge from previous studies or more general biologic insight should be integrated in the evaluation process[6].

Table 5.6 Distribution of influential baseline characteristics between trial medication groups

	Previous maintenance treatment with a beta blocker							
	No					Yes		
	All	P	N	M	C	All	P	N
Number of patients	338	84	89	79	86	177	81	96
Pain free interval								
< 1 hour	26%	23%	33%	23%	27%	25%	27%	23%
1–3 hours	36%	27%	36%	47%	34%	37%	35%	39%
> 3 hours	38%	50%	31%	30%	40%	38%	38%	39%
Baseline ECG								
Not codable	4%	6%	3%	3%	5%	3%	2%	4%
No ST ↓ ≥ 0·1 mV	83%	76%	88%	87%	79%	69%	63%	75%
ST ↓ ≥ 0·1 mV	13%	18%	9%	10%	16%	27%	35%	21%
Comparison of pain ECG with baseline ECG								
Not possible*	42%	46%	39%	33%	48%	46%	42%	50%
Same ST coding	17%	15%	19%	18%	14%	15%	16%	14%
More ST depression	31%	29%	30%	41%	26%	31%	33%	28%
More ST elevation	19%	17%	24%	19%	17%	20%	22%	19%
Both†	9%	7%	12%	10%	5%	12%	14%	10%
Estimated risk of RI/MI_{48}								
Low	64%	67%	60%	66%	65%	49%	42%	54%
Medium	25%	26%	22%	29%	23%	23%	22%	24%
High	11%	7%	18%	5%	12%	28%	36%	22%

P, placebo; N, nifedipine; M, metoprolol; C, combination: RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours.
* No pain observed after hospital admission or no (codable) baseline electrocardiogram available for comparison.
† More ST-segment depression in some leads and more ST-segment elevation in other leads.

Table 5.7 Adjusted rate ratios (with 95%-confidence intervals in brackets) for comparisons of index trial medications with placebo

	RI/MI_{48}	MI_{48}	MI_{1w}
No previous maintenance treatment with a beta blocker			
Nifedipine/placebo	1·15 (0·83, 1·64)	1·51 (0·87, 2·74)	1·55 (0·93, 2·73)
Metoprolol/placebo	0·76 (0·49, 1·16)	1·07 (0·54, 2·09)	1·17 (0·62, 2·18)
Combination/placebo	0·80 (0·53, 1·19)	0·88 (0·44, 1·74)	1·13 (0·62, 2·10)
On continued maintenance treatment with a beta blocker			
Nifedipine/placebo	0·68 (0·47, 0·97)	0·86 (0·45, 1·61)	1·06 (0·61, 1·79)

RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{1w}, myocardial infarction within one week.
Adjusted rate ratios are treatment effect estimates that have been adjusted for unbalanced distributions of baseline risk for recurrent ischaemia or myocardial infarction within 48 hours.

EFFECT MODIFICATION IN HINT

In view of the above considerations, we have adopted a conservative approach in the exploration of the HINT data for baseline characteristics that provide evidence for appreciable effect modification. To begin with, we have restricted ourselves to the

Table 5.8a Summary information for stratified analysis involving estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours. The information pertains to comparisons of nifedipine, metoprolol, combination with placebo among patients not on previous maintenance treatment with a beta blocker

	Placebo	Nifedipine	Metoprolol	Combination	Weight
Recurrent ischaemia or myocardial infarction within 48 hours					
All patients	37% (31/84)	47% (42/89)	28% (22/79)	30% (26/86)	
Estimated baseline risk					
Low	23% (13/56)	28% (15/53)	19% (10/52)	16% (9/56)	0·64
Medium	59% (13/22)	70% (14/20)	39% (9/23)	60% (12/20)	0·25
High	83% (5/6)	81% (13/16)	75% (3/4)	50% (5/10)	0·11
Standardized rate	38·6%	44·4%	30·2%	30·7%	
Rate ratio					
Adjusted via standardization		1·15	0·78	0·80	
Adjusted via M–N method		1·15 (0·83, 1·64)	0·76 (0·49, 1·16)	0·80 (0·53, 1.19)	
Crude		1·28 (0·90, 1·84)	0·75 (0·48, 1.18)	0·82 (0·53, 1·25)	
Myocardial infarction within 48 hours					
All patients	15% (13/84)	28% (25/89)	16% (13/79)	14% (12/86)	
Estimated baseline risk					
Low	5% (3/56)	15% (8/53)	12% (6/52)	7% (4/56)	0·64
Medium	36% (8/22)	30% (6/20)	22% (5/23)	25% (5/20)	0·25
High	33% (2/6)	69% (11/16)	50% (2/4)	30% (3/10)	0·11
Standardized rate	16·1%	24·6%	18·2%	14·1%	
Rate ratio					
Adjusted via standardization		1·52	1·13	0·87	
Adjusted via M–N method		1·51 (0·87, 2·74)	1·07 (0·54, 2·09)	0·88 (0·44, 1·74)	
Crude		1·82 (1·01, 3·31)	1·06 (0·53, 2·13)	0·90 (0·44, 1·84)	
Myocardial infarction within one week					
All patients	17% (14/84)	31% (28/89)	19% (15/79)	20% (17/86)	
Estimated baseline risk					
Low	5% (3/56)	17% (9/53)	13% (7/52)	13% (7/56)	0·64
Medium	36% (8/22)	35% (7/20)	22% (5/23)	30% (6/20)	0·25
High	50% (3/6)	75% (12/16)	75% (3/4)	40% (4/10)	0·11
Standardized rate	17·9%	27·7%	22·1%	19·8%	
Rate ratio					
Adjusted via standardization		1·55	1·23	1·11	
Adjusted via M–N method		1·55 (0·93, 2·73)	1·17 (0·62, 2·18)	1·13 (0·62, 2·10)	
Crude		1·89 (1·08, 3·34)	1·14 (0·59, 2·19)	1·19 (0·63, 2·24)	

M–N, Miettinen–Nurminen (see text).
Percentages are observed rates, with tallies in brackets.
Weights were taken proportional to overall stratum size among patients not on previous maintenance treatment with a beta blocker. The standardized rate ratio was obtained as the ratio of the standardized rates. Intervals in brackets indicate 95%-confidence intervals.

outcome event 'recurrent ischaemia or myocardial infarction within 48 hours', since the information with regard to myocardial infarction is too scanty to warrant subgroup analysis. Furthermore, the examination was limited to a few baseline characteristics that justified further inquiry into their effect modifying properties beforehand: (1) the (summary score for) baseline risk—for baseline risk is almost by definition a potential modifier; (2) the presence of in-hospital episodes of chest pain with established ST-segment or T-wave changes—for these patients more specifically represent the concept of unstable

Table 5.8b Summary information for stratified analysis involving estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours. The information pertains to the comparison of nifedipine with placebo among patients on continued maintenance treatment with a beta blocker

	Placebo	Nifedipine	Weight
Recurrent ischaemia or myocardial infarction within 48 hours			
All patients	51% (41/81)	30% (29/96)	
Estimated baseline risk			
Low	24% (8/34)	19% (10/52)	0·49
Medium	67% (12/18)	30% (7/23)	0·23
High	72% (21/29)	57% (12/21)	0·28
Standardized rate	47·3%	32·5%	
Rate ratio			
Adjusted via standardization		0·69	
Adjusted via M–N method		0·68 (0·47, 0·97)	
Crude		0·60 (0·41, 0·86)	
Myocardial infarction within 48 hours			
All patients	20% (16/81)	14% (13/96)	
Estimated baseline risk			
Low	9% (3/34)	8% (4/52)	0·49
Medium	11% (2/18)	9% (2/23)	0·23
High	38% (11/29)	33% (7/21)	0·28
Standardized rate	17·6%	15·2%	
Rate ratio			
Adjusted via standardization		0·86	
Adjusted via M–N method		0·86 (0·45, 1·61)	
Crude		0·69 (0·35, 1·33)	
Myocardial infarction within one week			
All patients	23% (19/81)	20% (19/96)	
Estimated baseline risk			
Low	9% (3/34)	12% (6/52)	0·49
Medium	22% (4/18)	9% (2/23)	0·23
High	41% (12/29)	52% (11/21)	0·28
Standardized rate	21·1%	22·4%	
Rate ratio			
Adjusted via standardization		1·06	
Adjusted via M–N method		1·06 (0·61, 1·79)	
Crude		0·84 (0·48, 1·48)	

M–N, Miettinen–Nurminen (see text).
Percentages are observed rates, with tallies in brackets.
Weights were taken proportional to overall stratum size among patients on continued maintenance treatment with a beta blocker. The standardized rate ratio was obtained as the ratio of the standardized rates. Intervals in brackets indicate 95%-confidence intervals.

angina and treatment effects may be more outspoken among these patients; (3) the presence of at least 0·1 mV segment depression either on the baseline or the pain electrocardiogram—for the same reasons as (2); (4) the presence of similar ST-segment elevation—for ST-segment elevation is known to be associated with coronary spasm, and nifedipine is known to have specific spasmolytic properties; (5) heart rate—

Table 5.9a Summary information to assess effect modifying properties of estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours. The information pertains to comparisons of nifedipine, metoprolol, combination with placebo among patients not on previous maintenance treatment with a beta blocker

	Placebo	Nifedipine		Metoprolol		Combination	
	Rate	Rate	RR	Rate	RR	Rate	RR
All patients	37% (31/84)	47% (42/89)	1·28*	28% (22/79)	0·75*	30% (26/86)	0·82*
Estimated baseline risk							
Low	23% (13/56)	28% (15/53)	1·22	19% (10/52)	0·83	16% (9/56)	0·69
Medium	59% (13/22)	70% (14/20)	1·18	39% (9/23)	0·66	60% (12/20)	1·02
High	83% (5/6)	81% (13/16)	0·98	75% (3/4)	0·90	50% (5/10)	0·60
Adjusted rate ratio			1·15		0·76		0·80

RR, rate ratio relative to placebo (*crude).
Percentages are observed rates of recurrent ischaemia or myocardial infarction within 48 hours, with tallies in brackets.
Adjusted rate ratios were obtained via the Miettinen–Nurminen method (see text).

Table 5.9b Summary information to assess effect modifying properties of estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours. The information pertains to the comparison of nifedipine with placebo among patients on continued maintenance treatment with a beta blocker

	Placebo	Nifedipine	
	Rate	Rate	RR
All patients	51% (41/81)	30% (29/96)	0·60*
Estimated baseline risk			
Low	24% (8/34)	19% (10/52)	0·82
Medium	67% (12/18)	30% (7/23)	0·46
High	72% (21/29)	57% (12/21)	0·79
Adjusted rate ratio			0·68

RR, rate ratio relative to placebo (* crude).
Percentages are observed rates of recurrent ischaemia or myocardial infarction within 48 hours, with tallies in brackets.
Adjusted rate ratios were obtained via the Miettinen–Nurminen method (see text).

for the chronotropic effect of beta blockade might be more salutary among patients with a high heart rate, whereas the tendency of nifedipine to cause a reflex tachycardia may offset potential benefits among these patients.

Tables 5.9a and 5.9b provide summary information that pertains to the exploration of effect modifying properties of the summary score for baseline risk. The stratum-specific rate ratios for recurrent ischaemia or myocardial infarction within 48 hours are consistent over the risk strata; this points to a uniform effect over the risk strata. Tables 5.10a and 5.10b show summary information with regard to (adjusted) rate ratios in the above defined subgroups. The stratum-specific rate ratios in patients with chest pain accompanied by ST-segment or T-wave changes indicate that the effect of metoprolol (or of the combination) may be more outspoken. The rate ratios in patients not on previous maintenance treatment with a beta blocker who present explicit ST-segment depression indicate that beta blockade alone is most effective, that nifedipine alone might have a more

outspoken negative effect, and that combination treatment may be ineffective. Among patients with ST-segment elevation no specific advantage for nifedipine was observed. Patients with a heart rate over 70 beats min^{-1} did not appear to benefit specifically from treatment with metoprolol. The salutary effect of nifedipine among patients on previous maintenance treatment with a beta blocker was hardly affected by the subgrouping, except for the presence of high heart rate, which appeared to attenuate the positive effect of nifedipine.

Discussion

This discussion pertains to the methodological aspects of the data analytic procedures. A general discussion of the trial findings is provided in chapter nine.

Clinical trials are carried out to provide empirical information to improve treatment of future patients. A physician takes a decision on treatment for an individual patient on the basis of a careful judgment of the expected therapeutic benefit against possible disadvantages and costs. Consequently, the objective of a clinical trial is to provide evidence with regard to the magnitude of the expected therapeutic benefit. The goal of data analysis is to extract the pertinent information from the data, in the form of estimates of the expected therapeutic benefit together with an indication of their precision. It is the task of the investigator to carry out data analysis and to report the resulting effect estimates, but conclusions (or better stated, incorporation of the evidence in the body of medical knowledge) should be left to the medical community.

The traditional statistical approach to data analysis in clinical trials based on statistical hypothesis testing is at odds with this principle. Hypothesis testing has been borrowed from the application of statistics in industrial quality control experiments, where one takes a random sample from a production batch, 'tests' it for some aspect of quality, and either 'reject' or 'accepts' the batch at issue, repeating the process as new (identical) batches come along. Based on this concept, *P*-values and hypothesis testing have been introduced (and have become accepted) as the cornerstone of inference in clinical research. Inference is presented in terms of testing a specified null-hypothesis (for example that the nifedipine and placebo rates for recurrent ischaemia are the same) against alternatives which are neither specified in direction nor in magnitude (the nifedipine rate differs from the placebo rate). Note that as far as hypothesis testing is concerned the magnitude of the effect is irrelevant: it has only relevance as far as the power of the study is concerned and therefore bears on study size but not on hypothesis testing after the data have been acquired. The argument then continues that, if the result is significant at some accepted level of the test (i.e., the *P*-value obtained is smaller than a prespecified value arbitrarily but conventionally set at 0·05) there is a departure from the null hypothesis. On the other hand, if the test is not significant, one accepts the null-hypothesis. While this seems to be an acceptable procedure for the above mentioned industrial quality control experiment, it is inappropriate for inference in the research setting. To begin with, unlike the situation in process industry, where the experimentor takes an actual decision (e.g. non-acceptance of the batch implies destruction of the batch), the clinical research investigator does not take a general decision on efficacy. [The absence of the need to take decisions in the research setting should not be confused with the need (for the treating physician) to take treatment decisions in individual patients!] Furthermore, whereas in process industry each inference independently pertains to the quality of its specific batch (produced under identical circumstances), inferences in different clinical trials with similar treatments in similar disease entities are interrelated. Hypothesis testing is based on the assumption that no other information relevant to inference is available, from whatever source. While this assumption probably holds in the industrial quality control setting, it does not apply to the research setting.

Why has such an unattractive methodology become so popular? Undoubtedly, its appeal derives from the apparent objectivity and definiteness of declaring observed differences 'statistically significant' or not. Scientific inference is reduced to a mechanical process: the presence of a treatment effect is established via a simple calculation. The process of statistical inference based on significance testing has little to do with the intellectual process of scientific inference (see chapter 2). Furthermore, the popularity of hypothesis testing is due to misinterpretations around the *P*-value concept. The *P*-value indicates the probability, that the observed rate ratio will depart from unity to the extent that was observed or more, assuming that the underlying risks are equal (i.e., assuming that no real differential treatment effect exists). The definition of the *P*-value is often formulated as 'the probability of the observed differences being due to chance' or something alike. This definition unjustly suggests that the *P*-value represents the probability that the compared treatments are equi-effective. It also leads to the

Table 5.10a Summary information to assess effect modifying properties of selected baseline characteristics. The information pertains to comparisons of nifedipine, metoprolol, combination with placebo among patients not on previous maintenance treatment with a beta blocker

	Recurrent ischaemia or myocardial infarction within 48 hours						
	Placebo	Nifedipine		Metoprolol		Combination	
	Rate	Rate	RR	Rate	RR	Rate	RR
All patients	37% (31/84)	47% (42/89)	1·15 (0·83, 1·64)	28% (22/79)	0·76 (0·49, 1·16)	30% (26/86)	0·80 (0·53, 1·19)
Patients with:							
Pain + ST–T changes* ($N = 172$)	59% (23/39)	60% (29/48)	0·98 (0·70, 1·39)	38% (18/47)	0·71 (0·44, 1·09)	47% (18/38)	0·78 (0·50, 1·17)
ST↓ $\geqslant$ 0·1 mV† ($N = 97$)	44% (12/27)	67% (14/21)	1·38 (0·85, 2.36)	29% (7/24)	0·66 (0·31, 1·26)	52% (13/25)	1·07 (0·64, 1·83)
ST↑ $\geqslant$ 0·1 mV† ($N = 87$)	45% (9/20)	57% (13/23)	1·03 (0·60, 1·99)	32% (7/22)	0·68 (0·31, 1·95)	18% (4/22)	0·39 (0.14, 1·04)
Heart rate $\geqslant$70 b min^{-1} ($N = 201$)	35% (18/52)	47% (27/57)	1·16 (0·77, 1·87)	32% (14/44)	0·85 (0·50, 1·44)	35% (17/48)	0·91 (0·56, 1·50)

Percentages are observed rates of recurrent ischaemia or myocardial infarction within 48 hours, with tallies in brackets underneath.
RR—Rate ratios are relative to placebo and are adjusted for estimated baseline risk (Miettinen–Nurminen method), with 95%-confidence intervals in brackets underneath.
* Patients with an in-hospital episode of chest pain with ST-segment or T-wave changes confirmed by the Classification Committee.
† Either in the baseline electrocardiogram or on the pain electrocardiogram.

incorrect notion that when statistical significance is observed (i.e. when $P < 0{\cdot}05$), one carries a 5% risk of falsely concluding that the treatment effects are different or, equivalently, that treatments effects are truly different in 95% of the instances when statistical significance is observed. Decision making in a statistical test is, to a certain extent, similar to decision making in a diagnostic test. Those who interpret statistical significance as proof of effect make the same mistake as those who accept an abnormal laboratory test as proof of disease. The 5% level of a statistical test is its false positive rate. A conventional statistical test thus has, by definition, a specificity of 95%. The power of a statistical test represents its sensitivity. The probability of taking the correct decision after the observation of a statistically significant outcome (a positive test) or after the observation of a nonsignificant outcome (a negative test) corresponds to predictive value in the setting of the diagnostic test. It therefore depends on sensitivity, specificity, and on prior opinion as well. To pretend that treatment effects would be truly different in 95% of instances when significance is observed amounts to misinterpretating the meaning of the 5% level of the statistical test.

In our data analysis we have refrained from statistical hypothesis testing and *P*-values altogether. Instead, we have provided readily interpretable point estimates of relative treatment effects with corresponding confidence intervals. These are a much better representation of the evidence contained in the data and should be used in all reporting of findings of clinical trials. Note in passing that *P*-values provide no additional information when presented in addition to a point estimate and a confidence interval.

It has been argued that in properly randomised trials imbalances in baseline characteristics found between treatment groups are to be viewed simply as a component of variability, duly reflected in the confidence interval[8]. When this view is adopted, data analysis ends with simple crude point and interval estimation. The opposite view is that one cannot rely blindly on randomisation to produce comparable treatment groups and that effect estimation should be valid (undistorted) conditional on the actual composition of the treatment groups. When this view is

Table 5.10b Summary information to assess effect modifying properties of selected baseline characteristics. The information pertains to the comparison of nifedipine with placebo among patients on continued maintenance treatment with a beta blocker

	Placebo	Nifedipine	
	Rate	Rate	RR
All patients	51% (41/81)	30% (29/96)	0·68 (0·47, 0·97)
Patients with:			
Pain + ST–T changes* ($N = 82$)	70% (30/43)	49% (19/39)	0·74 (0·50, 1·05)
ST↓ $\geqslant$ 0·1 mV† ($N = 69$)	72% (26/36)	48% (16/33)	0·73 (0·46, 1·08)
ST↑ $\geqslant$ 0·1 mV† ($N = 53$)	43% (9/21)	19% (6/32)	0·66 (0·30, 1·34)
Heart rate $\geqslant$ 70 b min^{-1} ($N = 60$)	46% (12/26)	38% (13/34)	0·88 (0·48, 1·61)

Percentages are observed rates of recurrent ischaemia or myocardial infarction within 48 hours with tallies in brackets underneath.
RR—Rate ratios are relative to placebo and are adjusted for estimated baseline risk (Miettinen–Nurminen method), with 95%-confidence intervals in brackets underneath.
* Patients with an in-hospital episode of chest pain with ST-segment or T-wave changes confirmed by the Classification Committee.
† Either on the baseline electrocardiogram or on the pain electrocardiogram.

adopted, simple analysis is only a starting point for further data analysis, which will involve stratification or multivariate analysis in an attempt to eliminate distortion that may have resulted from unevenly distributed baseline characteristics, if present. Clinical trial methodologists are divided over the need for and the interpretation of adjusted analyses. Simple or unadjusted analysis has an appealing simplicity and directness. Meier has made a strong case for regarding simple analysis as primary and 'avoiding the inevitable problems of interpretation which arise when the investigator is free to choose which baseline characteristics to report and to adjust for, thus introducing the possibility of even unintentional personal bias'[8]. On the other hand, one cannot expect the reader to give credence to simple effect estimates in instances in which randomisation has failed to create comparable treatment groups. Effect estimates that have been, to the best judgment of the investigator, adjusted for unbalanced baseline characteristics are an indispensable part in the analysis of clinical trial data, even if this approach renders the eventual estimates dependent on good and impartial judgment on the part of the investigator. In the end, it is to the reader and not to the investigator to cast judgment on the propriety of simple or stratified analysis. Of course, the problem is obviated when the two analyses yield approximately the same estimates. A study report should always present both analysis. Subjective judgment is often required to decide whether a crude (simple) estimate differs enough from an adjusted estimate to warrant stratified analysis. Note in passing that stratified analysis obviates the concept of 'failure of randomisation'. An unbalanced distribution of one or more influential baseline characteristics, which is sometimes called a 'failure of randomisation', does not invalidate treatment comparisons; it only requires to obtain adjusted effect estimates via appropriate stratification.

Assessment of baseline comparability explicitly amounts to comparing adjusted with (unadjusted) crude effect estimates. The traditional manner of assessing baseline comparability (in HINT, the application of statistical tests to the data of Table 5.6)

is meaningless: one knows beforehand that differences in baseline distribution must be attributed to chance. Furthermore, such tests disregard the impact of the imbalance on the effect estimates. From the methodological point of view, inclusion of this table is in fact superfluous; the table was nevertheless retained to link adjustment of effect estimation to the traditional way of assessing baseline comparability.

We have chosen the method of stratified analysis involving estimated baseline risk to evaluate and remove the distortion that is due to imbalance between the treatment groups in baseline risk. This method combines multivariate modelling (in the construction of the risk score) with stratified analysis (in the derivation of the treatment effect estimates). The advantages are the following: (1) the method explicitly deals with the intuitive concern for comparability of baseline risk; (2) treatment effects are expressed as readily interpretable rate ratios; and (3) the need (for the reader) to interpret a complex multivariate model is obviated. A further advantage is its relative lack of dependence on the usual assumptions underlying multivariate procedures: the fitted model is only required to provide a proper ranking by risk rather than its absolute assessment. There are also disadvantages: (1) the method has an ad hoc character and very little theoretical statistical work has been done to evaluate its performance; (2) it has been argued that the resulting confidence intervals are systematically too short[111] and (3) one carries the risk that not all distortion is eliminated. We are of the opinion that the advantage of transparency by far outweighs the alleged disadvantages.

An alternative approach would have been to obtain treatment effect estimates directly from the multivariate model. The weights (regression coefficients) for the trial medications in Table 5.11 of appendix I can be interpreted as trial medication effect estimates: their anti-logarithms represent the odds for developing the outcome event under index treatment divided by that under placebo. In the context of a clinical trial, however, the odds ratio is an unattractive measure.

When stratum-specific rate ratios differ widely between the strata—that is, when effect modification is apparently present—overall treatment effects become difficult to interpret. The focus of data presentation and analysis should shift from the estimation of overall effects to a description of the effect as a function of the baseline characteristic. This particularly applies to instances of qualitative effect modification—that is, when a positive treatment effect may be presumed to operate in one subgroup and a negative effect in another. There were no indications in the HINT data that this was the case.

It is a prevalent belief among statisticians that the interpretation of observations pertaining to the effect of one index treatment (relative to reference treatment) must be modified in the presence of other treatment arms: the multiple comparison problem. The aetiology of the alleged problem lies in the interpretation of *P*-values. When *P*-values are calculated for more than one treatment comparison, there is an increased probability that at least one *P*-value reaches statistical significance when in fact no differential treatment effects exist. This has led to the notion that the level of significance need be lowered according to some criterion. Note that his reasoning is based upon the understanding that the probability of *any* falsely significant finding must be kept below 0·05, in disregard of the implied increase in false negative rate (beta). The above notion also derives from considerations in industrial quality control experiments, where an instrument consisting of various components must be considered defective if one component is defective. The implied consequence would be, for instance, to broaden the confidence interval for the comparison of nifedipine to placebo just because additional data on other trial medications were collected in HINT. We fail to understand why (and how) the collection of additional data (on other treatments) should affect the precision of the effect estimate of nifedipine (relative to placebo). The ordinary 95%-confidence interval still has the property of containing the true treatment effect in 95% of cases. With this in mind, we have ignored the multiple comparisons problem and have obtained confidence intervals for each comparison of index trial medication with placebo as if it alone was the sole focus of the study.

HINT may look like having a so-called factorial design. One might entertain the idea that the effect of combination treatment (among patients not on previous maintenance treatment with a beta blocker) would be the combined effect of nifedipine and metoprolol. We have refrained from data analysis based on this principle. Because of the pharmacologic and haemodynamic interactions of nifedipine and metoprolol, the combination must be considered a separate drug whose effect is unrelated to that of nifedipine or metoprolol; hence its efficacy must be established independently. By the same argument, data on the treatment effect of nifedipine (relative to placebo) among patients on previous maintenance treatment with a beta blocker provide no information on the same comparison among patients without previous beta blockade.

We have not applied adjustments for the fact that the Policy Advisory Board has looked at the data as they accumulated on several occasions. This aspect is further discussed in chapter 7.

Appendix I: Multivariate modeling

BASIC PROPERTIES OF THE LINEAR LOGISTIC MODEL

The linear logistic model relates a probability (P) for developing the outcome event to the value of a baseline characteristic (X) using the linear logistic function:

$$\frac{1}{1 + e^{-(a+bX)}}.$$

Use of the logistic model assumes that, although every patient may have his own values of P and of X in the equation, the parameters (a and b) of that equation are characteristic for the population that patient belongs to. The above equation is referred to as a regression equation, which indicates that the variate X (the independent variate) is used to predict P (the dependent variate). Additional independent variates (X_1, X_2, etc. with corresponding coefficients b_1, b_2) can be accommodated in the model.

Alternatively, the logistic equation can be written as

$$\ln\left(\frac{P}{1 - P}\right) = a + bX.$$

The quantity $P/(1 - P)$ is the odds for developing the outcome event; the logarithm of the odds (i.e. the left hand side of the above equation) is referred to as a 'log odds' or as a 'logit'. Thus the use of a logistic model implies that the logit for developing the outcome event depends linearly on X.

From a set of observations on baseline characteristics $X_1, X_2, \ldots, X_n$ in a group of patients and the actual occurrences of the outcome events in those patients, the parameters of the model a, $b_1, b_2, \ldots, b_n$, which were characteristic for the patient group as a whole, can be estimated. For this purpose several techniques are available. Walker and Duncan's method of iterative solution of the unconditional maximum likelihood equation is generally advocated as the most reliable and is widely available in statistical computing packages.

FITTING A LOGISTIC MODEL TO DATA

In constructing a model, the first step is to translate the observed baseline characteristics into a set of statistical variates $X_1, X_2, \ldots, X_n$, which can be used in the regression model. As an example, previous myocardial infarction (a baseline characteristic with only two categories: present or absent) is represented by an indicator variate assuming the value 1 if previous myocardial infarction is present and 0 if otherwise. This variate actually 'indicates' the presence of previous myocardial infarction. The pain free interval (a baseline characteristic with three categories: less than one hour, between one and three hours, and greater than three hours) can be represented by two indicator variates: one indicating the category 'less than one hour' and one indicating the category 'between one and three hours'; the category 'greater than three hours' is implicitly indicated when both variates assume the value 0. It is also possible to involve the numeric value of the pain free interval as such in the logistic regression.

Forward selection and backward elimination are two commonly used methods for deciding which variates to include in the model. They are as automatic selection procedures widely available in statistical computing packages. In forward selection variates are sequentially entered into the model until no remaining candidate variate meets a specified entry criterion, usually a significance level. A backward elimination procedure starts with a model containing all possible variates, from which terms are sequentially eliminated. Many of the automatic selection procedures combine elements of forward selection and backward elimination. However, model fitting should never be a matter of automatic selection. Considerations of medical plausibility and interpretability of the coefficients should also play a role in the construction of the model.

MODEL FITTING IN HINT

The summary score for baseline risk represents the risk for developing the outcome event under placebo treatment. Yet, all patients may be included in the fitting procedure provided that (indicator) variates representing the patient's trial medication are kept in the model. (The baseline risk can be obtained by setting these variates to values representing placebo treatment (regardless of the patient's actual trial medication.) In this way, data on all patients are involved in the construction of the model.

A patient's trial medication was indicated as follows: one variate indicated previous maintenance treatment with a beta blocker; three variates indicated treatment with nifedipine, metoprolol, and the combination respectively in the absence of previous maintenance treatment with a beta blocker; another variate

Table 5.11 Indicator variates (with coefficients and standard errors) retained in the logistic model to predict the development of recurrent ischaemia or myocardial infarction within 48 hours and that to predict progression to myocardial infarction within 48 hours

	Prediction of:					
	RI/MI_{48}			MI_{48}		
Indicator	Coeff.	SE	Coeff./SE	Coeff.	SE	Coeff./SE
Nifedipine treatment	0·339	0·344	0·985	0·706	0·414	1·703
Metoprolol treatment	−0·612	0·369	−1·658	0·036	0·456	0·080
Combination treatment	−0·393	0·355	−1·107	−0·165	0·457	−0·362
Pre-treatment with a beta blocker	0·402	0·352	1·142	−0·040	0·447	−0·092
Addition of nifedipine	−0·807	0·351	−2·299	−0·236	0·444	−0·532
Pain free interval less than 1 hour	1·228	0·290	4·237	1·283	0·368	3·484
Pain free interval between 1–3 hours	0·414	0·254	1·632	0·537	0·348	1·542
Baseline ECG missing	0·246	0·533	0·460	1·262	0·587	2·151
ST depression $\geqslant$ 0·1 mV on baseline ECG	0·713	0·271	2·627	0·915	0·308	2·971
Pain ECG absent	−0·460	0·304	−1·514	0·029	0·408	0·072
More ST↓ during pain than at baseline	0·558	0·258	2·167	0·669	0·309	2·164
More ST↑ during pain than at baseline	0·731	0·271	2·696	0·774	0·304	2·545
Constant	−1·252	0·354	−3·536	−2·946	0·485	−6·073

RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; coeff., coefficient; SE, standard error.

indicated treatment with nifedipine in the presence of continued maintenance treatment with a beta blocker.

As a general principle only indicator variates were used to represent baseline characteristics. Continuous variables were divided into thirds (as for heart rate and blood pressure in Table 3.10) and indicator variates for two categories (as described above) were used. One variate was used to indicate that the ST-segment code on the baseline electrocardiogram was not available, in which case all other electrocardiographic variates were set to 0. Three variates were defined to indicate the presence of ST-segment depression of at least 0·1 mV, of similar ST-segment elevation, and of T-wave inversion of at least 0·10 mV on the baseline electrocardiogram. A separate variate was used to indicate that the ST-segment code on the pain electrocardiogram was not available, in which case all variates referring to the pain electrocardiogram were set to 0. Two variates to indicate a more severe coding for ST-segment depression and of ST-segment elevation on the pain electrocardiogram (relative to the baseline electrocardiogram) were defined. Enzyme values at baseline were not considered because they were not known to the clinician when he admitted the patient.

The model to describe the risk for developing recurrent ischaemia or myocardial infarction within 48 hours was fitted to the data of 515 patients without pre-randomisation myocardial infarction, using the PLR program from the BMDP statistical package. The standard PLR criteria of $P < 0{\cdot}10$ for inclusion and $P > 0{\cdot}15$ for elimination were applied. Model fitting was initially carried out within clusters of related baseline characteristics. Thereupon, those variates that were retrieved from the various clusters were collated into one final model. Selection was not followed mechanically. Variates representing trial medications (including representation of previous maintenance treatment with a beta blocker) were kept in the model, as were the two variates indicating that either the pain or the baseline electrocardiogram was missing. (As a consequence of the latter, regression information on electrocardiograms was extracted from those patients in whom the respective electrocardiogram was available.) A model to describe the risk for developing myocardial infarction within 48 hours was developed simultaneously.

Table 5.11 shows the variates that were eventually retained in the multivariate logistic model for the prediction of recurrent ischaemia or myocardial in-

farction within 48 hours with their coefficients and standard errors. The regression coefficients in Table 5.11 have a direct epidemiological meaning: each coefficient represents the log odds of developing recurrent ischaemia or myocardial infarction when all other factors are controlled. Its antilogarithm is the odds ratio of the event considered. As an example, the regression coefficient of 'ST-segment depression of at least than 0·1 mV on the baseline electrocardiogram' is 0·915; its antilogarithm ($e^{0·915}$) is 2·50. This means that the odds for developing ischaemia or myocardial infarction within 48 hours for patients with at least this amount of ST-segment depression is 2·5 times as high as it is for patients without it. Similarly, coefficients for trial medications can be interpreted as trial medication effect estimates (relative to corresponding placebo) expressed as odds ratios. Table 5.11 also shows the regression coefficients for the function to predict the occurrence of myocardial infarction within 48 hours.

ESTIMATION OF BASELINE RISK

The summary score to estimate baseline risk for recurrent ischaemia or myocardial infarction within 48 hours was obtained by setting the variates indicating the patient's actual trial medication to values (0) indicating treatment with placebo. Next, for an individual patient the coefficients from Table 5.9 that applied to that patient were added. From this sum, denoted as Z, the summary score was obtained as $\{1 + \exp(-Z)\}^{-1}$. As an example, for a patient on previous maintenance treatment with a beta blocker, with a pain free interval of less than one hour, with ST-segment depression of at least 0·1 mV at baseline, with more ST-segment depression during pain, without ST-segment elevations whatsoever Z was calculated as:

$$Z = -1·252 + 0·402 + 1·228 + 0·713 + 0·558 = 1·649.$$

and the summary score was 0·839 [$= \{1 + \exp(-1·649)\}^{-1}$]. Thus, a patient with this baseline profile has an estimated baseline risk of 84% for developing recurrent ischaemia or myocardial infarction within 48 hours. In other words, it is expected that 84% of patients with this profile will develop recurrent ischaemia or myocardial infarction within 48 hours (when initially treated with placebo).

Appendix II: Statistical calculations

In this appendix methods to obtain point estimates and confidence limits for the rate ratio are provided. A more elaborate description can be found elsewhere[6,7,9,12]. The 0·975 percentile of the Gauss distribution (1·960) is used throughout; the formulas thus apply to 95%-confidence limits only.

CONFIDENCE LIMITS FOR UNSTRATIFIED DATA

When the (unstratified) data are cast in the array shown in Table 5.1, the limits of the 95%-confidence interval for the risk ratio can be obtained as:

$$\left(\frac{r_1}{r_0}\right) 1 \pm 1·960 \Big/ \sqrt{X^2}$$

where X^2 is generally taken as the Mantel–Haenszel X^2 statistic, which is defined as:

$$X^2 = \frac{(r_1 - r_0)^2}{r(1-r)\left(\frac{n}{n-1}\right)\left(\frac{1}{n_1} + \frac{1}{n_0}\right)},$$

with $n = n_1 + n_0$ and $r = (a + b)/n$. This method is known as 'test-based'[10]. An alternative method is to calculate the limits of the 95%-confidence interval as:

$$\frac{r_1}{r_0} = \exp\left(\pm 1·960 \sqrt{\frac{1 - r_1}{a} + \frac{1 - r_0}{b}}\right).$$

This method, based on a log-transformation and an estimate of the standard error, has been recommended by Katz[13]. It was criticized by Miettinen because its propensity to yield poor results in extreme cases but also on theoretical grounds[1]. Miettinen and Nurminen have proposed a theoretically more attractive method[1]. Computer simulations indicated a better performance, but the formulas can only be solved iteratively.

POINT ESTIMATION FOR STRATIFIED DATA

It is assumed that k strata with group size n_{1j} and n_{0j} ($j = 1, 2, \ldots, k$) are available from which k stratum-specific index and reference rates r_{1j} and r_{0j} with corresponding rate ratios RR_j ($= r_{1j}/r_{0j}$) have been obtained.

The general principle underlying standardization is to combine the stratum-specific index rates into one overall index rate r_1^* and, similarly, the reference rates into one overall reference rate r_0^*, by taking weighted averages. The overall RR is obtained as $RR = r_1^*/r_0^*$. One may choose weights proportional to the overall size of the stratum; this approach is satisfactory if the treatment groups within each stratum have approximately equal sizes, which is usually the case in a randomised trial. However, it is more efficient to apply the weights proposed by Cochran, which are defined as $W_j = (n_{1j}^{-1} + n_{0j}^{-1})1$ for $j = 1, 2, \ldots, k$[14]. These weights reflect the comparative amount of information in $r_1^* - r_0^*$ under the assumption that index and reference rates are equal and constant over the strata. The rate ratio thus obtained is computationally equivalent to the so-called Mantel–Haenszel estimate of the risk ratio (e.g. formula 17.11 in Kleinbaum[9]).

The Miettinen–Nurminen estimate of the overall rate ratio chooses weights proportional to the comparative amount of information in $r_1^* - (RR \times r_0^*)$, conditional on the value of the rate ratio being estimated. These weights can only be obtained iteratively.

A different approach is to obtain stratum-specific rate ratios first and to obtain the overall rate ratio as weighted average of these stratum-specific rate ratios. As the distribution of ratio estimates is skew, it is conventional to use the logarithmic scale. The weights for pooling of the RR_j are usually taken as $W_j = (a_j b_j n_{1j} n_{0j})/[a_j(n_{0j} - b_j)n_{1j} + b_j(n_{1j} - a_j)n_{0j}]$, the inverse of the variance of $\ln RR_j$. The overall rate ratio is then obtained as

$$RR = \exp\left\{\left[\sum_j W_j \ln(RR_j)\right] \Big/ \sum_j W_j\right\}.$$

CONFIDENCE LIMITS FOR STRATIFIED DATA

Test based confidence limits for standardized rate ratios can be obtained as:

$$\left(\frac{r_1^*}{r_0^*}\right)^{1 \pm 1{\cdot}960 \Big/ \sqrt{X^2}}$$

where X^2 is defined as:

$$X^2 = \frac{(r_1^* - r_0^*)^2}{\sum_j W_j^2 r_j(1 - r_j)\left(\frac{n_j}{n_j - 1}\right)\left(\frac{1}{n_{1j}} + \frac{1}{n_{0j}}\right)}.$$

This statistic was, in a slightly different form, introduced by Cochran in 1954, who used the above mentioned (Cochran) weights[14]. With these weights, the formula is computationally equivalent to the well-known Mantel–Haenszel chi-square statistic[15] and is widely available in computer programs.

Standard error based confidence limits for standardized rate ratios are also available, see for instance Table 17.16 in Kleinbaum[9]. Confidence limits for the Miettinen–Nurminen point estimate have to be obtained iteratively[1].

When the overall rate ratio is obtained by pooling stratum-specific rate ratios, test-based confidence limits can be obtained as above; standard error based confidence limits are also available[9].

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Errata Appendix II

The first formula (page 67) reads as:

$$\left(\frac{r_1}{r_0}\right)^{1 \pm 1{\cdot}960/\sqrt{X^2}}$$

The third formula (page 67) reads as:

$$\frac{r_1}{r_0}\ \exp\left(\pm 1{\cdot}960\sqrt{\frac{1-r_1}{a}+\frac{1-r_0}{b}}\right).$$

The thirteenth line on page 68 (left column) reads as:

$n_{0j}^{-1})^{-1}$ for $j = 1, 2, \ldots, k$ [14]. These weights reflect

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6 Planning and conduct

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Background and history

The idea for HINT originated from clinicians working at the Thoraxcentre in 1979. A provisional protocol was approved by the Scientific Council of the Interuniversity Cardiology Institute of the Netherlands in 1980. Thereupon, Bayer GmbH, Germany, agreed to award a grant of Fl 500,000 to the Institute. Hässle AB, Sweden, offered additional funding for Fl 100,000. The Institute committed itself to provide further funding.

The university clinics that constituted the Interuniversity Cardiology Institute agreed to participate. Three non-university clinics were selected. The Policy Advisory Board was formed by the end of 1980. The Scientific Council of the Interuniversity Cardiology Institute together with the heads of the participating non-university Clinical Centres would act as Executive Committee. The Coordinating Centre was set up in the then newly established Clinical Epidemiology Unit of the Thoraxcentre.

Detailed planning and development of a trial protocol and forms continued until February 1981, when the first patient was enrolled. On 30 October 1984 enrolment was discontinued because an interim analysis suggested that the risk of myocardial infarction was higher in patients assigned to nifedipine than in patients treated with the other trial medications. Both Bayer and Hässle and the Dutch health authorities were informed of the decision but not of the actual data. A paper in which the main trial findings were described appeared in November 1986[1].

Trial organization

The HINT Research Group consisted of the following units: 11 Clinical Centres, the Coordinating Centre, the Executive Committee, the Technical Group, the Policy Advisory Board, and the Classification Committee. The Clinical Centres together with the Coordinating Centre were responsible for recruitment and treatment of patients and for collection and analysis of data. The other units were created in order to ensure proper conduct of the trial, quality of operations, and optimal communications not only among the centres but also towards the sponsors and the scientific community as a whole.

Eleven Clinical Centres, eight from university hospitals and three from non-university hospitals, were responsible for the enrolment of suitable patients, for the management of the patients, and for the collection of data. Two university clinics started in 1983, when their universities joined the Interuniversity Institute.

The Coordinating Centre was located at the Clinical Epidemiology Unit of the Thoraxcentre in Rotterdam. Its staff consisted of a trial coordinator, an associate trial coordinator, a database manager, and administrative personnel. The head of the Clinical Epidemiology Unit functioned as the director of the Coordinating Centre, who together with the trial coordinator provided scientific direction for the trial at the operational level. The tasks of the Coordinating Centre were to: (1) prepare, update, and maintain the trial protocol and corresponding forms; (2) work with the investigators in setting up local procedures for patient recruitment and data retrieval; (3) distribute prepacked trial medication; (4) collect and review data forms; (5) inform Clinical Centres of outstanding data forms or of incomplete or inconsistent items on submitted forms; (6) prepare patient reports for independent review by the Classification Committee; (7) prepared, update, and maintain the computer data base; (8) generate periodic reports evaluating the performance of the Clinical Centres; (9) perform the final data anlysis; (10) prepare the final trial report for approval by the research group as a whole. The staff of the Coordinating Centre was kept blinded to treatment assignment; it was neither informed of treatment monitoring reports. The director was an ex officio non-voting secretary to the Policy Advisory Board and was in the position to generate periodic (unblinded) treatment monitoring reports to the Policy Advisory Board.

The Executive Committee was composed of all members of the Scientific Council of the Interuniversity Cardiology Institute and of the principal investigators of the participating non-university Clinical Centres. The Executive Committee was the main

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leadership committee of the study. It had final responsibility for its scientific conduct. Its specific functions were to (1) establish the organizational structure; (2) select the Clinical Centres; (3) select the members of the Policy Advisory Board and those of the Classification Committee; (4) approve the study protocol; (5) approve necessary or desirable changes in the study protocol based on considerations of feasibility or practicability of design; (6) act upon recommendations from the Policy Advisory Board concerning major changes in study design; (7) review performance reports of the Clinical Centres; (8) act upon recommendations from the Policy Advisory Board in matters of early termination of one or more treatment arms; (9) resolve operational problems brought before by the Coordinating Centre; (10) approve study reports and papers for publication or presentation. The Executive Committee was not informed of treatment monitoring reports until the Policy Advisory Board recommended early termination. Meetings of the Executive Committee coincided with the monthly meetings of the Scientific Council.

The Policy Advisory Board was composed of representatives of the following disciplines: cardiology, epidemiology, pharmacology, ethics. Two members were appointed on the recommendation of the sponsors; these appointments were on personal title and required confidentiality. The Policy Advisory Board acted in a senior advisory capacity on policy matters to the Executive Committee. Its functions were to (1) provide final approval of the study protocol; (2) recommend changes in the study protocol (3) audit data collection and data processing; (4) advise on key issues regarding data analysis and publication. In addition, the Policy Advisory Board periodically reviewed treatment monitoring reports for evidence of adverse or beneficial trial medication effects. The Board was entitled to recommend early termination of one or more treatment arms to the Executive Committee. The Board met once a year, starting from November 1982. The initial review of the study plan was carried out in writing.

The Classification Committee was composed of three experienced cardiologists appointed by the Executive Committee. The trial coordinators acted as non-voting secretaries to the committee. The committee's task was to provide an independent medical review of clinical data with a view to ascertain eligibility and outcome events. Its members were kept blinded to trial medication assignments and were not informed of treatment monitoring reports.

The Technical Group was an informal body composed of nursing and medical personnel involved in the trial. This group met periodically to maintain a cohesive investigative group. Study progress and clinic performance were evaluated. The meetings also included tutoring sessions to outline patient selection, treatment, and data collection. No treatment monitoring reports were made available.

Funding of the trial

The agreement between the Interuniversity Cardiology Institute and the sponsors was based on the understanding that the trial organization would be completely independent from the sponsors. The Executive Committee had the authority to make major policy decisions, to terminate the study, and to decide on dissemination of the study findings. The sponsoring companies were informed of trial progress but not of unblinded treatment monitoring reports. When the study was terminated, the sponsors were fully informed of the findings and of the proposed plan for data analysis and publication.

The unrestricted Bayer grant of Fl 500,000 was designated to provide the university affiliated Clinical Centres with new technical equipment; the Hässle grant of Fl 100,000 was used to provide the non-university clinical centres with technical equipment required to carry out the trial procedures. The Clinical Centres did not receive further reimbursements of costs. The Interuniversity Cardiology Institute paid salaries of the personnel of the coordinating centre and further expenses as well. The funds of the Interuniversity Cardiology Institute are provided by the Dutch Ministry of Education.

Methods and quality control

PREPARATORY STEPS

Procedures describing the clinic operations and data intake were developed in advance in close collaboration with clinic personnel so as to fit clinic routine as closely as possible. The forms were in near final form when the study was started. Procedures for data processing were developed after the trial had been started.

The drugs and their placebo counterparts were supplied by Bayer GmbH of Germany (nifedipine) and by AB Hässle of Sweden (metoprolol). Packaging and labelling according to the randomisation code were done by the Pharmacy Department of Bayer. The stock was shipped to Bayer's subsidiary in the Netherlands and thence in limited supplies under supervision of Coordinating Centre to the Clinical Centres.

Once a Clinical Centre had agreed to participate, the study protocol was submitted to its Institutional Review Board. To explain the study procedures, sessions with clinic personnel were organized. Attention was also paid to the underlying principles of intervention research in general and to those of this trial in particular. One staff member, either a senior cardiologist or a senior fellow, was appointed local trial coordinator. He was responsible for the local execution of the trial. When the Centre was ready to begin, supplies of trial medication, manuals of procedures, and data forms were left at the coronary care unit.

PACKAGING AND LABELLING OF TRIAL MEDICATION

The nifedipine capsules were orange and contained 10 mg nifedipine; the corresponding placebo capsules were identical in appearance and taste. The metoprolol tablets and their corresponding placebo tablets were white and identical in appearance and taste. The tablets were dispensed in bottles so as to provide treatment for fourteen days.

Packages of trial medication were identified by their randomisation number. Randomisation numbers intended for patients not on previous maintenance treatment with a beta blocker consisted of a four letter code indicating the Clinical Centre followed by a three digit sequence number, e.g. AZUA-001; randomisation numbers for patients on maintenance treatment with a beta blocker were followed by a B, e.g. AZUA-001-B. Packages intended for patients not on maintenance treatment with a beta blocker had a white label and contained two bottles, one marked 'Nifedipin' the other 'Metoprolol'. Those for patients on maintenance treatment with a beta blocker had a blue label and contained one bottle, marked 'Nifedipin'. The bottles contained, in accordance with the randomisation code, either true medication or placebo. Each package also contained ten self-adhesive labels to identify study forms. Each package was complemented with a sealed envelope which contained the randomisation code. The randomisation number was printed on the package, on the bottles, and on the envelope.

For each Clinical Centre two sequences of treatment allocations were prepared in such a way that treatments were balanced for every twelve allocations. The schemes were generated by Bayer GmbH Germany after instructions of the director of the Coordinating Centre. Only two copies of the schemes were generated, one for the Pharmacy Department of Bayer to carry out the packing and one for the director of the Coordinating Centre.

PATIENT RECRUITMENT AND ENROLMENT

A specially designed admission form was made available (Table 6.1). Its purpose was to guide the treating physician through the (complex) enrolment process. The form consisted of numbered series of questions and instructions with categorized answers. Answers were given by ticking the appropriate box. Each box contained a number to indicate the next item or the word 'stop' to indicate 'ineligibility'. The instructions were devised in such a way that the treating physician was prompted to undertake the right actions, to check the inclusion and exclusion criteria, and to record the requested data. The form was self-explaining and obviated consultations of the manual. Eligibility was established in items 8 to 16. If unstable angina was conjectured but did not satisfy the HINT criteria, the respective patient was labelled as potential candidate who might qualify if a new episode of chest pain should occur (item 13). After consent had been obtained (item 17) and eligibility had been verified (item 18), patients were placed into the appropriate stratum defined by previous maintenance treatment with a beta blocker and assigned to a randomisation number (items 19 to 21). After baseline measurements had been obtained (item 22), the first dose of trial medication was handed out (item 23). It was required to register new entries immediately by mailing a registration form to the Coordinating Centre.

RECORDING OF FOLLOW-UP DATA

Execution of trial procedures after randomisation hinged on the case record form, which provided instructions on patient management, measurements, and observations. Key information on episodes of chest pain, other clinical events, the administration of drugs, electrocardiography, blood sampling, heart rate, and blood pressure was recorded on the case record form. Electrocardiograms were recorded in duplicate. Measurements of activities of cardiac enzymes and were recorded separately, as were angiographic findings.

SITE VISITS AND DATA COLLECTION

Coordinating Centre staff paid regular site visits to the Clinical Centres. Central to the site visit was the meeting with the local trial coordinator. For each randomised patient all data forms and related records were scrutinized for completeness and consistency. Uncertainties were clarified. The local coordinator was asked an opinion as to whether recurrent ischaemia or myocardial infarction had occurred within 48 hours of randomisation. The occurrence of

Table 6.1 The admission form (in English translation). The part of the form in which demographic date were recorded (items 1–6) and in which the general exclusion criteria were checked (item 7) is not reproduced here

8. Tick the appropriate and continue from there.
   Unstable angina was diagnosed
   - ○ Upon admission to hospital.
     Did the patient have chest pain at that time? — yes [14] no [9]
   - ○ After an attack of chest pain in the hospital.
     Describe clinical course from hospital admission until now: _____
     _____ GO TO [14]
   - ○ After normal enzyme values (in patients originally diagnosed as suspected infarction).
     Was chest pain observed in the hospital — yes [15] no [9]

9. Is there a recent history of typical angina at rest or during light activity, lasting > 15 min? — yes [10] no [13]

10. Did the last episode of chest pain occur within the last 12 hours? — yes [11] no [13]

11. Does the electrocardiogram obtained at hospital admission show ST-T abnormalities typical for reversible myocardial ischaemia? — yes [16] no [12]

12. Is there any other evidence for atherosclerotic coronary disease? — yes [16] no [13]
    If yes, tick the appropriate.
    - ○ Previous myocardial infarction (documented).
    - ○ Previous episode(s) of unstable angina (documented).
    - ○ At least 50% narrowing of a major coronary artery observed at earlier angiography.

13. WAIT until chest pain with ST-T changes occurs.
    Did this occur? — yes [14] no [stop]
    If yes, on_____
    If no, the patient was discharged at:_____

14. Chest pain was treated as follows: (denote time)
    - ○ Obtain an electrocardiogram _____
    - ○ Give sublingual glyceryl trinitrate (0.5 mg) _____
    - ○ Give sublingual glyceryl trinitrate (0.5 mg) _____
    - ○ Give an intravenous injection of glyceryl trinitrate (max 1 mg in 10 ml 5% glucose) _____
    - ○ Give an intravenous injection of fentanyl (0.05 mg) _____

    Obtain electrocardiograms after each step. — yes [15] no [stop]
    Chest pain could be relieved.
    Obtain a blood sample.

15. The electrocardiograms show a pattern of ST-T changes suggesting reversible ischaemia. — yes [16] no [13]

16. Are you of the opinion that the patient sustains acute myocardial infarction at present? — yes [stop] no [17]

17. Inform the patient about the nature of the trial and ask consent. Informed consent was granted — yes [18] no [stop]

18. The patient can be admitted to the trial. Was the patient in fact admitted? — yes [19] no [stop]

ASSIGNMENT OF TRIAL MEDICATION

19. Was the patient on maintenance treatment with a beta blocker for more than three days? — yes [20] no [21]

20. OPEN the next BLUE MEDICATION BOX, with the label:
'On maintenance treatment with a beta blocker.'
The number of the box is: _____-B.
The patient will also be treated with two 100 mg doses of metoprolol per 24 hours.

GO TO 22

21. OPEN the next WHITE MEDICATION BOX, with the label:
'Not on maintenance treatment with a beta blocker.'
The number of the box is:_____

22. Perform baseline measurements.

23. START TRIAL MEDICATION.
(If applicable: start both drugs simultaneously)
Trial medication was started on _____ at _____ hours.

24. Fill out the registration form and mail it to the Coordinating Centre as soon as possible.
Add this form to the patient's clinical records.

acute myocardial infarction or death after 48 hours was ascertained from the clinical case notes. A copy of the patient's letter of discharge from the hospital was obtained. Stocks of trial medication and study forms were checked and replenished. Certain procedures were reviewed to prevent protocol violations recurring. Private discussions with clinic personnel were held to assess their practices and philosophy with regard to the study.

Patient forms and other study records were

transferred to the Coordinating Centre, where they were checked once more. Queries for additional information were sent to the local trial coordinator as needed.

ACTUAL CLINIC PERFORMANCE

The admission forms were sometimes filled out in retrospect after the patient had been entered. The registration form was mostly not immediately sent to the Coordinating Centre. Therefore, site visits were pivotal in the administration of the study. It occurred that trial medication was issued but that the patient concerned could not be identified; this constituted an unassessable enrolment (see chapter 3). None of the involved randomisation codes was broken. Case record forms were, generally speaking, filled out at the bed side, but in some Clinical Centres they were retrospectively filled out from routine records. Coronary angiography was scheduled at the earliest convenience but could mostly not be performed within one week, which was required by the study protocol.

THE CLASSIFICATION PROCEDURE

Each case was reviewed on the basis of a patient report prepared by the study coordinators. A narrative section summarized key information on the patient's history, the events that led to admission to hospital and those that occurred during 48 hour follow-up. Copies of all electrocardiograms and a survey of available enzyme values (until 54 hours) were added to the report. No information on events after 48 hours was provided. No reference whatsoever was made to the patients's treatment assignment.

The Classification Committee first decided whether electrocardiograms during chest pain were available. Next, judgment was cast on the presence of qualifying ST-segment or T-wave changes or abnormalities, and unequivocal violations of the admission protocol were noted. Thereafter, outcome events were ascertained. The review was first carried out in writing. Cases that elicited difference of opinion were discussed in plenary meetings. This was necessary for 60% of cases. Decisions by majority vote were necessary twice. All cases of myocardial infarction were re-examined after termination of the trial, so as to determine the onset of infarction and to describe electrocardiographic abnormalities which had developed after randomisation.

DATABASE MANAGEMENT

The study database consisted of all data contained on official data forms and supportive records that were collected for study purposes, such as electrocardiograms, queries, letters of discharge, angiography reports, annotations, classification reports. There was one folder for each patient that contained all paper records. The files were stored in locked cabinets at the offices occupied by the Coordinating Centre.

The computer database consisted of all codified information in the study database. A menu-oriented database management system was developed and maintained. Database management has been described in greater detail elsewhere[2]. The database consisted of a series of subfiles containing related information. The file containing patient identifying information was separated from the other files and was only accessible to authorized personnel. Patient identifying information was not used on data listings. A segregated file containing the randomisation codes was only accessible to the programmer who designed and maintained the general structure of the database but who was not involved in actual data management.

As a general principle, codification of (clinical) patient data was carried out by staff of the Coordinating Centre, using the narrative section of the classification report as the central source of information. This provided an extra opportunity for quality control. Provisos for automated data processing were intentionally left out from clinic forms. The codified information was recorded on mark sense cards. The system provided error reports on missing data, out-of-range data, and internal inconsistencies within a patient's data. Quantitative information, e.g. heart rates and blood pressures, was keyed into the computer via a menu oriented program. Codified information of selected electrocardiogram(s) was also recorded on marked sense cards[2].

For statistical analysis a separate analysis database was created on the central computing facilities of the Erasmus university of Rotterdam using SPSS-X and BMDP software. The analysis database was also extensively checked for internal consistency. The randomisation codes were added to the analysis database (but not to any paper records) after termination of the study. Corrections to the database were applied without knowledge of the randomisation code. The SPSS-X version of the analysis database was used for most statistical analyses. Logistic regressions was carried out using the BMDP version.

Discussion

Internal validity of a clinical trial first of all rests

on a sound study design. But an improper procedural implementation of an otherwise valid design may compromise (internal) validity. It may lead to effect estimates that systematically misrepresent the true treatment effects. Validity of a procedure can only be ascertained judgmentally by critical scrutiny of the procedures at issue and not from the data. We have elaborated on the procedural implementation of HINT to provide the reader a basis for judging the quality of the evidence.

Random allocation of treatments is the most crucial procedural feature of a clinical trial. Validity of the randomisation procedure is largely unrelated to the issue of baseline comparability because it is impossible to distinguish between inappropriate randomisation and chance as the cause of an imbalance between treatment groups. Random allocation of treatment in HINT was carried out via pre-packed trial medication, the usual procedure in double-blind evaluation of drugs. No mismatches between the randomisation code and the actual content of the packages were found. The pills (true or placebo) were indistinguishable in appearance and taste. One problem, however, was detected shortly after the trial was started: the randomisation code could be obtained by holding the accompanying envelope (for emergencies) against bright light. This was immediately corrected. Otherwise, there were no possibilities to obtain the randomisation code in advance (or after randomisation) without being detected.

Today, it is widely recommended that eligible patients be irrevocably registered before randomisation[3]. This is of vital interest in an open comparison of, say, surgical treatment with continued pharmacologic treatment. The register is supposed to record the exact moment of randomisation and hence the beginning of the follow-up period for all randomised patients. In the context of a double blind comparison of drugs, the procedure seems less urgently needed. Selective withdrawal would not occur unless randomisation codes were broken. In HINT we have opted for registration by mail immediately after randomisation. This procedure did not function well. It has led to unassessable enrolments. This flaw does not compromise internal validity because no randomisation codes were broken. It seems reasonable to assume that these mistakes were not guided by specific knowledge of the treatment given.

The difficulties and hazards of carrying out a complex trial protocol in patients with an acute illness have been recognized from the very beginning. We have taken explicit measures to enhance protocol adherence and to avoid unnecessary violations of the study protocol. The trial forms were designed to be self-explanatory. Furthermore, Coordinating Centre staff made site visits to the Clinical Centres to discuss each enrolment and to evaluate trial proceedings and data recording. Errors were noticed immediately, and corrective measures could be taken as needed. Measures were taken to secure high level performance of the Classification Committee. Guidelines for the review were drafted in advance. All electrocardiograms were meticulously studied. No information whatsoever on trial medication actually used was available to the Classification Committee. The Policy Advisory Board functioned as an independent audit committee to monitor quality of operations within the Coordinating Centre. All codified information in the computer database was independently verified from the original records. The analysis database was extensively checked for missing data, correct ranges, and internal consistency.

A close link between the sponsoring pharmaceutical industry and the trial institutions may compromise validity. The agreement between the sponsoring companies and the Interuniversity Cardiology Institute virtually denied any influence of the sponsors on the conduct of the study. This also applied to the phase of data analysis and reporting of the findings. The Policy Advisory Board was a completely independent body—the membership of two appointees on behalf of the sponsors was on personal title and was subject to confidentiality. All staff members of the Coordinating Centre were employed by the Interuniversity Cardiology Institute of the Netherlands.

In summary, we are convinced that we have conducted this trial, which is concerned with an acute clinical condition, in a manner that complied with the highest possible standards of procedural implementation.

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7 Progress monitoring and termination

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Predetermined study size

The Executive Committee decided in advance that 150 patients per trial medication group among patients not on previous maintenance treatment with a beta blocker ought to be enrolled. No specific study size was determined for patients on previous maintenance treatment with a beta blocker. The decision was taken on the presumption that 600 patients not on previous maintenance treatment with a beta blocker could be accrued over a period of two years. The decision was taken after a series of so-called power calculations had been made. The power calculations are reproduced in appendix III (page 86).

Progress monitoring

Progress of the study was reported to the Executive Committee once a month. Corrective actions were initiated when necessary; these measures included the addition of new Clinical Centres to boost patient accrual, protocol amendments to eliminate inconsistent or unclear issues, and the exertion of peer pressure to encourage Clinical Centres with poor performance records to improve.

The Policy Advisory Board served as an external advisory–review group. This task was combined with that of monitoring treatment effects. The board reviewed study progress in an annual site visit to the Coordinating Centre. The study plan and associated procedures, patient accrual, protocol adherence, data collection and processing were scrutinized. The (unblinded) treatment monitoring report was reviewed in a private meeting with the director of the Coordinating Centre. No pre-specified stopping rule was adopted. The review sessions were followed by a joint meeting with the Executive Committee, in which the Policy Advisory Board reported its findings and made recommendations on continuation of the study and other important policy issues. Table 7.1 shows the data of the various treatment monitoring reports.

The first meeting of the Policy Advisory Board took place on 13 November 1982, when 227 patients had been enrolled. The study plan was re-examined. The board rejected the policy of the unchanged continuation of previous maintenance treatment with a beta blocker; instead, continuation with two doses of 100 mg metoprolol was proposed. The board recommended to continue the study for at least another year. The Executive Committee agreed to to these recommendations. The second meeting of the Policy Advisory Board was held on 3 December 1983, when 517 patients had been enrolled. The board expressed its worry about the many protocol violations and about the slackening accrual rate; at least two additional Clinical Centres ought to be involved in the study. The board recommended to continue the study as scheduled. However, the board also requested that a treatment monitoring report be prepared and mailed to them after six months. The third interim report was mailed to the members of the Policy Advisory Board on 30 July 1984. In the mean time, the Scientific Council of the Inter-university Institute had decided to allow continuation of the study until the first of May 1985 at the utmost. After telephonic consultations with the director of the Coordinating Centre, the board recommended continuation of the study until that date. An extra meeting was scheduled in conjuction with a conference in Rome on 27 October 1984. The main purpose of that meeting was to discuss dissemination of the findings after termination of the study. Based on the data of the interim report on that occasion (fourth panel in Table 7.1) the Policy Advisory Board reached the conclusion that patient accrual ought to be terminated immediately. The full text of the recommendation to the Executive Committee is reproduced in appendix I (page 82). The Executive Committee agreed, and measures to discontinue patient inclusion were put into effect immediately. The Executive Committee issued a public announcement (see appendix II, page 83). It was forwarded to the Dutch Health authorities and to the Dutch branches of Bayer and Hässle.

Conclusion of the Study

When HINT was terminated, reports and data on 75 patients were in preparation. The reports were finalized and reviewed most expeditiously. Codification of electrocardiograms, which was in its early phase only, was accelerated. The Classification re-examined the data on all patients with myocardial

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Table 7.1 Outcome event rates in trial medication groups at four interim analyses

			Outcome events		
	MI_0	*No* MI_0	*RI*/MI_{48}	MI_{48}	MI_{1w}
No previous treatment with a beta blocker					
First interim analysis:					
Placebo	4	28	12 (43%)	3 (11%)	
Nifedipine	6	25	8 (32%)	4 (16%)	
Metoprolol	9	23	8 (39%)	2 (9%)	
Combination	3	29	9 (26%)	4 (12%)	
Second interim analysis:					
Placebo	5	55	17 (31%)	7 (13%)	
Nifedipine	6	57	27 (47%)	16 (28%)	
Metoprolol	5	53	17 (32%)	11 (21%)	
Combination	4	59	20 (34%)	11 (19%)	
Third interim analysis:					
Placebo	7	74	25 (34%)	10 (14%)	11 (15%)
Nifedipine	6	73	31 (42%)	17 (23%)	21 (29%)
Metoprolol	6	70	21 (30%)	13 (19%)	14 (20%)
Combination	5	72	24 (33%)	12 (17%)	14 (19%)
Fourth interim analysis:					
Placebo	7	86	30 (35%)	12 (14%)	13 (15%)
Nifedipine	7	95	41 (43%)	26 (27%)	30 (32%)
Metoprolol	6	89	28 (31%)	17 (19%)	18 (20%)
Combination	7	88	30 (34%)	16 (18%)	18 (20%)
Final overall data:					
Placebo	6	99	37 (37%)	17 (17%)	18 (18%)
Nifedipine	6	107	50 (47%)	29 (27%)	33 (31%)
Metoprolol	8	103	33 (32%)	20 (19%)	22 (21%)
Combination	9	102	32 (31%)	16 (16%)	21 (21%)
On continued maintenance treatment with a beta blocker					
First interim analysis:					
Placebo	1	37	22 (59%)	5 (14%)	
Nifedipine	4	37	12 (32%)	3 (8%)	
Second interim analysis:					
Placebo	5	62	26 (42%)	8 (13%)	
Nifedipine	1	71	23 (32%)	7 (10%)	
Third interim analysis:					
Placebo	5	80	36 (45%)	14 (18%)	16 (20%)
Nifedipine	1	83	28 (34%)	10 (12%)	15 (18%)
Fourth interim analysis:					
Placebo	5	96	44 (46%)	18 (19%)	21 (22%)
Nifedipine	3	104	35 (34%)	15 (14%)	22 (21%)
Final overall data:					
Placebo	7	104	50 (48%)	19 (18%)	22 (21%)
Nifedipine	2	115	36 (31%)	16 (14%)	23 (20%)

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infaction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{1w}, myocardial infarction within one week.
First interim analysis: on 13 November 1982; 227 patients.
Second interim analysis: on 3 December 1983; 383 patients.
Third interim analysis: on 30 July 1984; 428 patients; by mail.
Fourth interim analysis: on 27 October 1984; 593 patients.
Final overall data: data on 668 patients, including those in whom an unequivocal protocol violation had occurred before randomisation.
A few second admissions were erroneously tallied in the fourth interim report.
Outcome event rates were based upon formal outcome assessments by the Classification Committee except for the first interim analysis, which was based upon an informal assessment by the local study coordinator.

infarction. The plan for data analysis was presented to the principal investigators on 31 January 1985 and subsequently to the involved pharmaceutical companies.

The Policy Advisory Board convened on 21 May 1985 to review the proposed plan for data analysis. The board stressed that patients in whom an unequivocal violation of the admission protocol had occurred did not have unstable angina as defined; they ought to be excluded because inclusion would hamper generalization. Furthermore, considering that the pain free interval (a very influential baseline characteristic) appeared unevenly distributed, the board recommended to continue the search for influential baseline characteristics and to apply appropriate stratification in the estimation of treatment effects. (The data of the codified electrocardiograms were not yet available at that time.) Both recommendations were supported by the Executive Committee.

The main findings of the study were disclosed in a meeting of the Dutch Cardiac Society in December 1985. The main study report was drafted in collaboration with the local investigators; the final version was approved by the principal investigators and the members of the Policy Advisory Board. It was confidentially made available to the involved pharmaceutical industries. It appeared in the November 1986 issue of the British Heart Journal. The present publication is a final and more elaborate account of HINT operations and findings. Further publications on electrocardiographic and angiographic findings are in preparation. Furthermore, findings on long-term follow-up will be reported.

Discussion

Enrolment in HINT was terminated on 30 October 1984 because an interim analysis suggested that the risk of myocardial infarction was higher in patients assigned to nifedipine than in patients treated with the other trial medications (among patients not on previous maintenance treatment with a beta blocker). The other treatment arms were also discontinued because effects in the other groups were smaller than expected.

Has HINT been terminated too early? We are of the opinion that it is unethical to continue a trial to produce unequivocal evidence of harm of a certain treatment. It suffices to exclude a minimal but relevant therapeutic benefit. Therefore, early termination of the nifedipine treatment arm among patients not on previous maintenance treatment with a beta blocker was by all means justifiable. On the other hand, continuation of the other trial medication groups would have provided valuable additional information. But the beneficial effects of the involved index trial medications as they eventually appeared were not so prominent at the time when patient enrolment was discontinued.

No additional data analytic support was requested (or provided) when it was decided to terminate the study. At that time the analysis database was not organized to the degree that adjusted effect estimates could have been provided. The study organization may be criticized for this. An important decision such as early termination of a large clinical trial should only be taken after thorough analysis of all available data.

Inspection of the interim reports together with the final data leaves the impression that the treatment effects as they appeared have been reasonably stable from the second analysis onward. The data suggest that the trial was terminated at the time when the negative effect for nifedipine (among patients not on previous maintenance treatment with a beta blocker) was most outspoken. The negative effect as observed at the fourth interim analysis, which led to early termination of the trial, was attenuated when the remaining cases were added to the tallies. This is probably due a 'regression to the mean' phenomenon. So far as effect estimates obtained from trials that were terminated ahead of time are biased, a natural correction occurred in this case.

As regards the interpretation of findings from a prematurely terminated trial, one should keep in mind that early termination, generally speaking, only occurs if the accumulating data suggest a treatment effect that deviates from what was expected, either in a positive or negative sense. The final view on the magnitude of the treatment effect, an update of prior views in the light of the data at hand, will hence lie between what was previously known and what is suggested by the data. Thus, prior views tend to attenuate treatment effects suggested by trials that were terminated ahead of time.

The Policy Advisory Board did not define a statistical stopping rule in advance. Statistical stopping rules are almost exclusively formulated in terms of hypothesis testing. Even if one were to accept the underlying principles, the problems for trials with more than two treatments have not satisfactorily been solved [1]. The stringency of the stopping criterion would be dependent on the number of compared treatments, which is unacceptable from the ethical point of view. A statistical stopping rule requires that

all contingencies are specified in advance, which is unrealistic. Decisions on early termination involve many nonstatistical issues. Statistical stopping rules do not reflect the complexity of stopping a clinical trial in practice. Given these unsolved—and in our view insoluble—problems, no attempt was undertaken to define or to use a formal stopping rule. Instead, the Executive Committee relied on the board's judgment as to whether it would be useful and ethical to continue the study.

What are the implications of treatment monitoring procedures for data analysis and inference? The traditional statistical approach is based upon the contention that the complete stopping rule is known, which then can be used to calculate so-called sequentially adjusted *P*-values. For example, the Beta Blocker Heart Attack Trial (BHAT) was prematurely terminated when the statistical stopping criterion was met.[2] The *P*-value obtained from the data was 0.001. However, when the stopping rule was taken into account, the results were only statistically significant at the 5% level. Had the same data been obtained in a trial with the actual size and follow-up planned in advance, the *P*-value would have been 0·001. In this reasoning, the interpretation of the data not only depends on what was actually observed but also on tentative actions that would have been undertaken by the investigator had other outcomes occurred. It is our impression that the evidence provided by the BHAT study is nevertheless taken at face value from the data only. This attitude is exemplified in the practice of meta-analyses: in a review of trials of beta blockers in myocardial infarction[3], Yusuf and Peto did not take account of the stopping rules of the trials concerned (e.g. of BHAT). It is apparently common sense that the interpretation of the data is not dependent on how the investigator monitored the data while the data were accumulated. A dependence of interpretation on stopping rules seems a violation of common sense.

This common sense feeling has a formal basis in statistical theory: the so-called likelihood principle implies that the interpretation of observations should only be based on what was observed; the sequential stopping rule that may or may not have been followed is irrelevant as far as the interpretation of the data is concerned[4–6]. It has been argued that data analysis that takes account of the stopping rule is a 'hoax'[6]. If one accepts the *P*-value as an appropriate basis for inference, then clearly data analysis would be dependent on the stopping rule. Thus, the traditional inference based on *P*-values is fundamentally at odds with the likelihood principle and with common sense as well. This is another reason to reject *P*-values and statistical hypothesis testing.

We have based our data analysis on point estimates and confidence intervals. As the formal (statistical) definition of the confidence interval is tied to statistical hypothesis testing, the confidence interval may also be dependent on the stopping rule. Consequently, data analysis based on confidence intervals would not accord with the likelihood principle and hence not with common sense. Perhaps, it is possible to put the definition of the confidence interval on a new (theoretical) footing in such a way that it accords with the likelihood principle, e.g. as a Bayesian posterior distribution. This would obviate the dependence of the confidence interval on the stopping rule. Unfortunately, no workable solutions have yet been provided by formal statistical theory. Our pragmatic solution has been to present point and interval estimates without accounting for the interim monitoring.

As regards predetermined study size, it is impossible to determine the optimal size of the treatment groups in a clinical trial statistically. The size of the groups in the present study was essentially determined judgmentally on intuitive grounds. The power calculations only provided additional support in establishing the size of the trial medication groups. The power calculations presented in Table 7.1 exemplify the instability of these calculations. The four specified alternative hypotheses are not that much different—but they are associated with substantially different power. Any group size between 75 and 300 patients can be obtained as a result of statistical size calculations by slightly altering the specified rates. Note in passing, that the power calculations are not needed to appreciate the amount of information in the data: the width of the confidence intervals already specified the precision of the effect estimates.

Appendix I: Report of the Policy Advisory Board to the Executive Committee on early termination of HINT

I. PREAMBLE

Upon reviewing the updated data on the Holland Interuniversity Nifedipine/metoprolol Trial in its meeting on 27 October 1984, the Policy Advisory Board reached, for the first time, the following conclusions:

(1) that in patients admitted to hospital for unstable angina pectoris in the absence of treatment with beta

blocking agents at the time, treatment with nifedipine without metoprolol is conducive to increased risk of non-fatal myocardial infarction;
(2) that treatment with metoprolol alone as well as the combination treatment, while not apparently counterproductive, seem unlikely to be efficacious in the prevention of myocardial infarction in these patients;
(3) that in unstable angina patients admitted to hospital while on beta blocking treatment, addition of nifedipine appears to be neither counterproductive nor efficacious in the prevention of myocardial infarction.

II. RECOMMENDATIONS

Given these conclusions by the Policy Advisory Board, it is imperative that the Executive Committee determine without any undue delay (and possibly with recourse to whatever data and consultations it deems relevant) to what extent it agrees with the Policy Advisory Board's conclusions.

Assuming that the Executive Committee comes to essential agreement with the Policy Advisory Board, the following recommendations for action are offered:
(1) that patient enrolment in the study be terminated at this time;
(2) that the manufacturer of nifedipine and the Dutch drug regulatory agency be informed, without any delay, about the Policy Advisory Board's conclusions (see preamble above) and of any possible dissent by the Executive Committee;
(3) that the content of those communications as well as of any responses to all inquiries (by colleagues, the media, the manufacturer, etc.) be confined to (a) citation of the conclusions statement of the Policy Advisory Board given in the preamble of this report, and (b) reference to the upcoming full report in a scientific journal:
(4) that the scientific report regarding the main objectives of the study be prepared and published most expeditiously with a view to making the results public at the earliest possible time consistent with the use of an appropriate forum; this report is to reflect input from all principal investigators, and the penultimate manuscript should be distributed to them, and to the Policy Advisory Board, no later than January 31, 1985;
(5) that no data bearing on relative merits of the treatments compared in the study be made public prior to the main report;
(6) that the manuscript of the main report, prepared in consultation with the Policy Advisory Board, be submitted to the manufacturers and to the Dutch drug regulatory agency immediately upon its acceptance for public presentation;
(7) that the Coordinating Centre submit within the next two weeks to both the Policy Advisory Board and the Executive Committee an outline of the result displays that it plans to produce (in order that members of these committees may provide their suggestions).

Appendix II: Public announcement issued by the Executive Committee after early termination of HINT

ANNOUNCEMENT 1 NOVEMBER 1984

The Holland Interuniversity Nifedipine/metoprolol Trial (HINT) has been carried out under the auspices of the Interuniversity Cardiology Institute of the Netherlands since 1981. The coronary care units of all university hospitals together with those of three non-university clinical centres participate in this study. The objective of this randomised, double blind, placebo controlled trial is to determine whether nifedipine (a calcium antagonist) or metoprolol (a beta blocker) prevent recurrence of ischaemia or progression to myocardial infarction when given to patients diagnosed as having unstable angina at admission to the care unit. Unstable angina is defined as the occurrence of chest pain which lasts for at least 15 minutes in combination with objective signs and symptoms of ischaemia of the myocardium, provided that outward signs of acute myocardial infarction are absent.

When the study was started a Policy Advisory Board, composed of international experts who were in no other way involved with the study, was instituted in order to counsel the Executive Committee with regard to the progress of the study. Its members are the cardiologists M. E. Bertrand, C. R. Conti, D. G. Julian, A. Vedin, the pharmacologist E. L. Noach, and the epidemiologist O. S. Miettinen.

On 11 October 1984, 675 patients had been enrolled in the study. Based on an interim analysis of data on 593 patients, the Policy Advisory Board, in its meeting of 27 October 1984, had reached the following conclusions.

1. that in patients admitted to hospital for unstable angina, in the absence of treatment with beta blocking agents at the time (of entry in the study) treatment with nifedipine without metoprolol is conducive to increased risk of non-fatal myocardial infarction;

2. that treatment with metoprolol alone as well as with the combination, while not apparently

counter-productive, seems unlikely to be efficacious in the prevention of myocardial infarction in these patients;

3. that in patients admitted to hospital while on beta blocker treatment addition of nifedipine appears to be neither counterproductive nor efficacious in the prevention of myocardial infarction.

Because of these conclusions of the Policy Advisory Board, the Scientific Council of the Interuniversity Cardiology Institute of the Netherlands has, in its meeting of 30 October 1984, decided to discontinue patient enrolment as of today. This decision has been taken after consultations with the participating non-university Clinical Centres.

The trial data are now being further analyzed. Until the analysis is completed (this is expected before 31 January 1985) and a report that presents the findings and describes the conclusions is accepted for publication, no further announcements will be made.

Appendix III: Statistical power calculations

The power calculations were carried out on the basis of expected rates for recurrent ischaemia or myocardial infarction within 48 hours among patients not on previous maintenance treatment with a beta blocker. The (statistical) null-hypothesis is that the expected rate in all four trial medication groups is the same. This hypothesis could be tested using the standard chi-square test for a two by four contingency table. Four so-called alternative hypotheses were considered: (A) the placebo rate is 40%, either of the two trial medications brings this rate down to 20%, the combination to 10%; (B) the placebo rate is 22·5%, either of the two trial medications brings this rate down to 15%, the combination to 10%; (C) the placebo rate is 30%, one of the two trial medications brings this down to 10%, the other trial medication is ineffective, either alone or in combination; (D) the placebo rate is 30%, none of the trial medications alone is effective but the combination brings the rate down to 10%. Under any of these hypotheses, the chi-square statistic follows a non-central chi-square distribution. The noncentrality parameter can be calculated from the specified alternative hypothesis[7]. Table 7.2 shows the calculated statistical power for each specified alternative hypothesis when 30, 50, 70, 100, and 150 patients would be assigned to each trial medication group. The upper panel shows the power calculations for testing at the conventional 5% significance level; the lower for testing at the 1% level. The choice of the rates under the four alternative hypotheses was based on a hunch

Table 7.2 Statistical power (%) of the chi-square test (for significance levels of 5% and 1%) for four alternative hypotheses (A–D) with various trial medication group sizes (N)

	Expected rates for RI/MI_{48}				Statistical power				
Hypothesis*	Pla	Nif	Met	Com	$N = 30$	$N = 50$	$N = 70$	$N = 100$	$N = 150$
5% level of significance									
A	40%	20%	20%	10%	66%	89%	97%	97%	>99%
B	23%	15%	15%	10%	15%	28%	34%	50%	69%
C	30%	10%	30%	10%	62%	86%	95%	99%	99%
D	30%	30%	30%	10%	42%	65%	81%	93%	99%
1% level of significance									
A	40%	20%	20%	10%	43%	73%	90%	98%	>99%
B	23%	15%	15%	10%	5%	12%	15%	27%	46%
C	30%	10%	30%	10%	38%	68%	86%	97%	>99%
D	30%	30%	30%	10%	21%	42%	61%	82%	96%

* Hypotheses A–D as defined in appendix III.

RI/MI_{48}, Recurrent ischaemia or myocardial infraction within 48 hours; Pla, placebo; Nif, nifedipine; Met, metoprolol; Com, combination of nifedipine and metoprolol.

By way of illustration, the third line of the first panel reads as follows: If nifedipine would reduce a placebo rate of 30% to 10% and if metoprolol would be ineffective, one would have a 62% chance of obtaining a statistically significant ($P < 0·05$) result in a trial with 30 patients per trial medication group; this probability becomes 99% in a trial with at least 100 patients per trial medication group.

of the involved clinicians; no specific data were available.

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8 Review of other trials

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Introduction

The primary task of a physician is to cure illness and to relieve suffering. Clinical research is motivated by the wish to improve and facilitate treatment of future patients. Much of the argument around clinical trial design, analysis, and interpretation focuses on questions of internal validity and statistics. It should not be forgotten, however, that valid and precise estimation of the treatment effect within the context of the clinical trial is meaningless by itself and is never, as such, the ultimate research objective. Rather, it is a means of achieving an objective, the objective being to provide empirical evidence of the usefulness of a particular treatment used for a particular indication. Thus clinical trials should not only be judged on their validity and precision. To be relevant, meaningful generalization should be possible—that is, the findings should support conclusions about the therapeutic benefit to be expected in a defined clinical indication which can be recognized in the reality of every day medical practice. This clinical indication derives from the disease entity actually studied in the clinical trial. It is stressed that 'disease entity' and 'clinical indication' in this context refer not only to a generic type of disease or illness but also to a particular stage in its development.

Generalization hinges on three issues: (1) the patients actually studied have to be representative for the indication at issue; (2) the study treatments must be representative for its eventual use in clinical practice; (3) the disease outcome(s) under study must represent clinically relevant objectives for therapeutic intervention.

Regrettably, little attention is generally given to the first of the above issues. The disease entity actually studied in a given clinical trial is determined by who was 'caught' by the patient enrolment procedure. The usual inclusion and exclusion criteria (even if they are well defined and described, which is not always the case) are aspects of this procedure but rarely define the indication studied completely. The medical environment where the trial is done also plays a role. Thus the descriptive profile of actually enrolled patients is of critical importance in assessing which indication they represent. Confusion about generalization will result if there is the slightest room for uncertainty about this profile and the way it came about.

Appropriate generalization further depends on the conceptual homogeneity of the disease entity. As an example, generalization is extremely difficult, if not impossible, from an unstable angina trial which included patients with recently developed symptoms, patients with refractory symptoms, and patients with stabilized symptoms as well—for these patients represent three physiologically and clinically distinct categories of unstable angina with different therapeutic objectives. The overall findings may certainly not indiscriminately be generalized to each of the three indications.

Confusion about the nature of the disease entity studied, and consequently about the indication to which the findings may be generalized, seems to be particularly a feature of clinical trials in acute cardiac patients. This is hardly surprising.

Some, but not all, patients with prolonged anginal pain at rest will develop objective evidence for myocardial infarction (necrosis) within a few hours. Other will sustain an attack of reversible ischaemia without subsequent myocardial necrosis. With current diagnostic methods it is impossible to reliably differentiate between the two at hospital admission. No matter how 'typical' the clinical picture at hospital admission may be for either condition, diagnostic certainty about its exact nature can only come from subsequent serial electrocardiograms and cardiac enzyme assessments. The latter in particular take several hours to become abnormal in patients with evolving myocardial infarction.

Given the rapidly changing nature of the relevant diagnostic and other clinical information, it is particularly difficult to specify the defining characteristics of a treatment indication arising during the first hours or days after the onset of symptoms of prolonged anginal pain at rest. As a result, clinical investigators in this field have apparently found it difficult to design enrolment procedures which define recognizable clinical indications. The major complicating factor is that the initiation of treatment often cannot and should not be delayed until the exact nature of the underlying condition has been clarified. As an example, it makes little sense to delay infarct size limiting treatment until all diagnostic

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criteria for acute myocardial infarction are met, or to attempt to prevent progression to myocardial infarction in a patient with suspected unstable angina if already evolving myocardial infarction must be excluded first by enzyme tests (which require six hours to become positive in infarction and in many instances much longer owing to laboratory delay).

In order to discuss the significance of recent trials in patients with prolonged anginal pain at rest, it is helpful to group them according to the clinical indications under study in relation to their defining characteristics and the relevant disease outcomes. We propose, and will use below, the classification drawn up in Table 8.1 for trials starting after hospital admission. (Prehospital trials are a category by themselves and are outside this scope.) This tabulation was devised so as to reflect the reality of clinical diagnosis and treatment decisions at the coronary care unit. It is our opinion that trials in this field should be designed so as to fit specifically in one of these general categories—for inclusion of an unspecified (or even a specified) 'mix' of patients from different categories will pose insurmountable problems in generalization. It must furthermore be stressed that trials within each general category are, of necessity, restricted to only one part of its clinical spectrum. Inclusion may be deliberately restricted to a specific subtype only. Even if this is not the case, restriction occurs because patients are excluded when either an accepted indication or a contra-indication for the investigational treatment exist, or when other concomitant disease is present, etc.

Apart from these specific restrictions, which will vary from trial to trial and will impose constraints on generalization, there are general constraints for each of the above categories that must be borne in mind.

In a trial in *suspected unstable angina* the in-

Table 8.1 Categorization of clinical trials in patients admitted to hospital for prolonged anginal pain at rest

Disease entity (indication)	Defining characteristics	Disease outcomes
For trials started immediately at hospital admission		
Suspected unstable angina	Chest pain at rest and electrocardiograms suggestive of reversible ischaemia No enzyme assessments required	Short-term recurrence of chest pain Progression to myocardial infarction and its sequelae
Suspected acute myocardial infarction	Chest pain and electrocardiograms suggestive of acute myocardial infarction; No enzyme assessments required	Enzymatic infarct size Left ventricular function Clinical outcome: Eventual diagnosis Complications Mortality
For trials started later during hospital stay		
Confirmed unstable angina after stabilization of symptoms	Recent chest pain at rest with ECG suggestive of reversible ischaemia >24 hours relief of chest pain No significant enzyme rises No new Q-wave formation	Recurrence of angina Occurrence of myocardial infarction Mortality Progression of coronary atherosclerosis
Confirmed unstable angina; unstable clinical condition (refractory angina)	Recurrent episodes of chest pain No signs of evolving myocardial infarction	Short-term recurrence of chest pain Progression to myocardial infarction
Confirmed acute myocardial infarction; stable clinical condition	Electrocardiograms and enzymes typical for myocardial infarction	Recurrence of myocardial infarction Mortality Progression of coronary atherosclerosis
Complications of acute myocardial infarction	Post infarction angina Arrhythmias Heart failure Cardiogenic shock etc	Subsequent clinical course

vestigators intend to study the effect of a particular treatment in patients who are suffering from attacks of reversible angina; patients who already experience evolving myocardial infarction are *excluded* as much as possible. In contrast, in a trial in *suspected acute myocardial infarction* the investigators intend to *include* only patients with evolving myocardial infarction. The distinction (in an individual patient) between reversible ischaemia and necrosis can only be made subsequently on the basis of serial enzyme assessments (hours after relief of chest pain) and electrocardiograms (days after the attacks). Thus, it is inevitable that patients with evolving myocardial infarction will be included in a trial in suspected unstable angina and vice versa. It follows that the eventual diagnosis of infarction, as such, is a relevant outcome in assessing treatment effects in both types of trials. However, later subgrouping based on the final diagnosis is inadmissable as far as internal validity is concerned—for the phenomena that make up the final diagnosis (serial electrocardiograms and enzyme assessments) occur after randomisation and may have been influenced by the study treatment. Such subgrouping would also be irrelevant as far as generalization is concerned: treatment recommendations can be based only on past and present symptoms and signs, not on those of the future.

Trials in patients with *confirmed unstable angina after stabilization of symptoms* are restricted to patients in whom myocardial ischaemia was considered to have been the cause of the presenting symptoms but in whom necrosis subsequent to the last anginal attack was excluded on the basis of repeat normal enzyme levels. The diagnosis at hospital admission is irrelevant: patients admitted under the diagnosis of suspected acute myocardial infarction may end up in this type of trial when enzymes turn out to be normal. Furthermore, it is important to know which treatments were prescribed at entry because the indication signifies in this instance success of treatment that was started to alleviate the presenting symptoms. Many trials of this type have a follow-up extending beyond hospital stay and therefore resemble to a certain extent the secondary prevention trials in post-infarction patients.

Confirmed unstable angina in continued unstable condition (i.e. recurring attacks of anginal pain) forms a well recognized indication for further pharmacologic or invasive treatment. Refractory angina belongs to this category. Trials would be specifically restricted to patients in whom myocardial ischaemia is considered to be the cause of the continuing symptoms and in whom enzymatic or electrocardiographic evidence has remained negative for evolving infarction. The diagnosis at hospital admission is to a large extent irrelevant: a patient admitted under the diagnosis 'suspected acute myocardial infarction' may end up in a study like this when enzyme values turn out to remain normal. In design, trials in these disease entities resemble those in suspected unstable angina at hospital admission with one important proviso: the continued instability represents an inherent failure of the treatment which was given up to the moment of randomisation. Thus, the nature of the treatment already given at entry may interact with the effect of the investigational treatment in a variety of ways, and generalization is conditional not only on the nature of the clinical condition in the patients who were actually enrolled but also on the treatment(s) given before entry. It is noted that this principle also applies to trials starting at hospital admission in reference to treatment that may have been used before, for instance when unstable angina develops in patients already being treated for stable angina.

With regard to trials in patients with confirmed recent myocardial infarction, there is generally little debate about what constitutes clinical proof of infarction, although one may argue about the specific electrocardiographic and enzymatic criteria. Thus any patient who develops such proof becomes a candidate for this type of trial. Again, the initial diagnosis at hospital admission is irrelevant as far as eligibility is concerned. These trials take the form of the well-known postinfarction or secondary prevention trial, in which patients are usually treated and followed for prolonged periods of time.

Another category of trials in confirmed recent myocardial infarction is designed to evaluate therapeutic measures for *complications of acute myocardial infarction* (e.g. postinfarction angina, arrhythmias, heart failure, or cardiogenic shock).

Methods

In this review we limit ourselves to randomised trials whose findings may be directly related to the findings of HINT. These include trials of nifedipine or beta blockade in suspected unstable angina or in suspected acute myocardial infarction and further trials in confirmed unstable angina after stabilization of symptoms.

The main features and findings of recent trials are summarized in tabular form. They are grouped in accordance with the scheme presented in Table 8.1.

Table 8.2 Summary findings of the Muller trial of nifedipine versus conventional treatment in suspected unstable angina[3]

	Treatment	
	Conventional	Nifedipine
All patients		
Failure of treatment*	27% (17/63)	30% (19/63)
Rate ratio	1·12	
95%-confidence interval	(0·64, 1·94)	
Myocardial infarction†	14% (9/63)	14% (9/63)
Rate ratio	1·00	
95%-confidence interval	(0·43, 2·31)	
Patients not on previous maintenance treatment with a beta blocker		
48 h recurrence of chest pain	34% (11/32)	70% (19/27)
Rate ratio	2·05	
95%-confidence interval	(1·22, 3·61)	
Patients with previous maintenance treatment with a beta blocker		
48 h recurrence of chest pain	81% (25/31)	50% (18/36)
Rate ratio	0·62	
95%-confidence interval	(0·41, 0·89)	

Percentages are observed rates, with tallies in brackets.
* A 'failure of treatment' occurred if chest pain continued to occur within 48 hours of the last increase in the original assigned treatment, or if the treatment was discontinued for side-effects.
† Within 14 days, as evidenced by raised enzyme values.

Unstable angina: an episode of chest pain within the last 24 hours, not exceeding 45 min in duration, and considered characteristic of unstable angina, provided that either electrocardiographic evidence of reversible ischaemia or other evidence of coronary artery disease was present and that no electrocardiographic or enzymatic evidence of acute myocardial infarction was present.

Treatment: Nifedipine treatment consisted initially of four 20 mg doses per 24 hour; conventional treatment of a combination of propranolol four 20 mg doses per 24 hours and isosorbide dinitrate four 10 mg doses per 24 hours. If propranolol was not acceptable, conventional treatment consisted of isosorbide dinitrate only. A double-dummy technique was used. Previous maintenance treatment with a beta blocker was continued, irrespective of trial medication assignment. If chest pain recurred, the dosage was (in two steps) increased to maximally four 30 mg doses nifedipine or to four 60 mg doses propranolol and four 20 mg doses isosorbide dinitrate per 24 hours, provided that no adverse effects occurred. If the maximal dosages did not eliminate chest pain, the other treatment was added.

There is a separate section about trials which could not be grouped according to this scheme.

As a summary of the evidence, the rates of the main disease outcomes are given for the index and reference groups, together with the rate ratio and its 95%-confidence interval, the latter calculated according to the method provided by Miettinen and Nurminen[1]. All rates are on intention-to-treat basis, for eligible patients. Mortality rates are for 'all-cause' mortality.

It has become fashionable of late to talk about 'meta-analyses' in this context and define this as a new type of research[2]. But there is nothing really new: clinicians confronted with trial results have always been required implicitly to weigh the new evidence in the context of prior opinions about the credibility of the mechanism of action involved and already existing empirical evidence, including that from other trials.

To resolve the confusion created by apparently conflicting results from different trials, meta-analysis relies on the pooling of results from different trials by statistical methods. At first sight this may look attractive: it seems advantageous to have one 'bottom-line' confidence interval (or *P*-value) to supplement the confusing array of different values from the individual trials. While meta-analyses start correctly from the premise that all available evidence must be taken into account, there is justifiable concern about the premises of statistical pooling. Furthermore, one is confronted here with a problem that is not only statistical in nature. Generalization of findings from clinical trials is a process which goes beyond statistical inference (see chapter 2). as is application of findings to medical practice. Therefore we shall do without formal statistical pooling.

Findings from trials in suspected unstable angina

In 1984 Muller and co-workers published findings of a randomised placebo-controlled trial designed to assess the effect of initial treatment with nifedipine (relative to conventional treatment) in eliminating recurrent chest pain and in preventing myocardial infarction in patients admitted to hospital with suspected unstable angina (Table 8.2)[3]. Unstable angina was defined as chest pain at rest (details are in Table 8.2). Patients were randomised to receive treatment with nifedipine or conventional treatment consisting of isosorbide dinitrate and propranolol (details in Table 8.2). If chest pain recurred, dosages were (in two steps) increased; if the maximal dosages did not eliminate chest pain, the other treatment was added. The report does not explicitly mention whether randomisation was delayed until at least one series of enzyme values was available. Of 133 random-

ised patients four were identified by the creatine kinase core laboratory as having experienced myocardial infarction immediately before randomisation and another four patients were found not to have met the electrocardiographic inclusion criteria, leaving a total of 126 patients available for effect assessment. 'Failure of treatment' was defined as chest pain at the maximal original treatment level or severe adverse effects and occurred to the same extent in the two treatment groups. This was also the case for progression to myocardial infarction within 14 days. The authors also reported that 'in the subgroup of patients who were on maintenance treatment with propranolol treatment with nifedipine controlled pain more rapidly than did nitrates and (if not contra-indicated) propranolol'; on the other hand, 'in the subgroup of patients who were not on maintenance treatment with a beta blocker nitrates and (if not contra-indicated) propranolol controlled pain more rapidly than did nifedipine'. These statements are based on comparisons of curves that indicate the cumulative incidence of being pain free for at least 48 hours. Rates for 'failure of treatment' were not given for each mode of previous maintenance treatment with a beta blocker separately. However, rates for 'recurrence of chest pain within 48 hours' could be derived from these curves. They are summarized in the lower part of Table 8.2.

Findings from trials in suspected acute myocardial infarction

NIFEDIPINE

Table 8.3 shows design features and major findings from four randomised placebo-controlled trials designed to evaluate the effect of nifedipine in suspected acute myocardial infarction. All trials have included patients presenting with symptoms and signs typical for acute myocardial infarction. In most trials predefined electrocardiographic abnormalities were required for patient eligibility. Progression to myocardial infarction, infarct size as determined by enzyme kinetics, and mortality were the main outcomes. All trials excluded patients on maintenance nifedipine treatment.

Muller and co-workers randomised 171 patients who were retrospectively categorized: patients with pre-randomisation enzyme rises or new Q-wave formation were grouped as 'acute myocardial infarction'; the remaining patients were grouped as 'threatened myocardial infarction'[4]. No differences in rates of progression to myocardial infarction or infarct size indices emerged from the comparison. The higher two-week mortality for nifedipine patients vanishes when six-month mortality rates are taken into account. Rates of myocardial infarction were also equal among patients with threatened myocardial infarction only: 75% in both treatment groups. Sirnes and co-workers reported the results of the Norwegian Nifedipine Multicenter Trial, which included 222 patients[5]. In this trial nifedipine appeared not to influence progression to myocardial infarction, enzymatic infarct size, or mortality. Branagan and co-workers reported findings from a small trial with 98 patients[6]. Wilcox and co-workers reported on the TRENT study (trial of nifedipine in acute myocardial infarction), in which 4491 patients were included[7]. No data on infarct size were collected. Twenty-eight days mortality rates were virtually identical for the two treatment groups. The effect of nifedipine was not related to previous beta blockade.

BETA BLOCKERS

A great number of trials with different beta blockers (given either orally or intravenously or both ways) in suspected acute myocardial infarction have been performed. Most of them were quite small and not especially designed at comparing mortality rates. Yusuf et al and Hjalmarson have provided useful reviews[8,9]. We limit ourselves to two major large-scale trials with short-term mortality as primary outcome, whose findings dominate.

Table 8.4 summarizes the main design features and results of the Metoprolol in Acute Myocardial Infarction (MIAMI) trial and the more recently published, but otherwise concurrent, First International Study of Infarct Survival (ISIS-1) trial[10,11]. Patients not on previous beta blockade were admitted within 24 and 12 hours respectively of an episode of chest pain thought to be characteristic for acute myocardial infarction. Study treatment was started intravenously and was continued orally thereafter. MIAMI was a double-blind study. ISIS-1 provided an open comparison against a policy to refrain from beta blockers as much as possible. The observed treatment effects were almost identical: rate ratios of 0·87 and 0·86, respectively. When the data of all other available trials of early beta blockade (starting with an intravenous dose) were pooled (together approximately 6000 patients), the same trend was observed[11]. The percentage of patients in whom eventually evidence for myocardial necrosis was established was not affected by either treatment. It must be noted, however, that a small difference

Table 8.3 Summary of four placebo-controlled trials of nifedipine in suspected acute myocardial infarction

	Trial			
	Muller[4]	Sirnes[5]	Branagan[6]	TRENT[7]
Design features				
Year of publication	1984	1984	1986	1986
Dosage nifedipine (mg per 24 h)	120	50	40	40
Start of treatment	< 6 h	< 12 h	—	< 24
Start of treatment	78% > 3 h	5 h (mean)	3 h (mean)	7 h (mean)
Follow-up	14 days	6 weeks	4 days	28 days
Total number of patients	171	222	98	4491
Outcomes				
Myocardial infarction *				
Nifedipine	84% (75/89)	67% (74/110)	61% (28/46)	64% (1429/2240)
Placebo	85% (70/82)	74% (83/112)	44% (23/52)	64% (1442/2251)
Rate ratio	0·99	0·91	1·38	1·00
95%-confidence interval	(0·86, 1·13)	(0·76, 1·08)	(0·94, 2·04)	(0·95, 1·04)
Infarct size index †				
Nifedipine	14·1	25	710	—
Placebo	14·3	23	655	—
Ratio	0·99	1·09	1·08	—
Mortality ‡				
Nifedipine	10·1% (9/89)	9·1% (10/110)	10·9% (5/46)	6·7% (150/2240)
Placebo	8·5% (7/82)	8·9% (10/112)	9·6% (5/52)	6·3% (141/2251)
Rate ratio	1·18	1·02	1·13	1·07
95%-confidence interval	(0·48, 2·96)	(0·45, 2·30)	(0·37, 3·47)	(0·86, 1·33)

Percentages are observed rates, with tallies in brackets.
* The development of enzymatic or electrocardiographic signs of acute myocardial infarction within 48 hours of randomisation; Muller also provided percentages for patients without raised enzyme values at randomisation: 75% in both treatment groups.
† Peak MB-creatine kinase release; the means of the Muller study pertain to all patients (0 was substituted for patients without raised enzyme values); those of the other studies pertain to patients with raised enzyme values only.
‡ Mortality figures relate to six months (Muller), six weeks (Sirnes), and one month (TRENT and Branagan) periods. Muller also provided mortality figures for 14 days; these were 0% for placebo and 8% for nifedipine.

was observed in MIAMI patients who were randomised within seven hours of onset of chest pain.

Of the smaller trials two deserve special mention—for they included patients with 'threatened infarction'. In 1978 Norris and co-workers reported on a trial on the 'protective effect of propranolol in threatened myocardial infarction'[12]. Threatened infarction was defined as chest pain typical for myocardial infarction in the absence of ST-segment elevations greater than 0·2 mV in the precordial leads or 0·1 mV in the inferior leads. Patients with established unstable angina were excluded. Patient were assigned at random 'by the envelope method' to receive propranolol or no beta blockade. The main outcome event was the development of raised creatine kinase levels. The rates were 55% (11/20) for propranolol and 97% (22/23) for reference patients. The rate ratio was 0·58; 95%-confidence interval: (0·35, 0·81).

In 1983 Yusuf reported findings in patients with threatened infarction (defined as above) which were randomised to receive atenolol (76 patients) or no beta blockade (94 patients)[13]. Patients with electrocardiographic signs of evolving myocardial infarction were also randomised: 168 patients to atenolol and 139 to placebo. Irregularities during randomisation with 'the envelope method' were reported. The rates for infarction within ten days among patients with threatened infarction were 49% (37/76) for atenolol and 66% (62/94) for placebo. The rate ratio was 0·74; 95%-confidence interval: (0·55, 0·96).

Findings from trials in confirmed unstable angina after stabilization of symptoms

Table 8·5 summarizes design features of two trials designed to evaluate protective effects of acetyl

Table 8.4 Summary of two selected controlled trials of beta blockade in suspected acute myocardial infarction

	Trial	
	MIAMI[10]	ISIS-1[11]
Design features		
Year of publication	1985	1986
Index treatment	Metoprolol	Atenolol
Dosage (mg per 24 hours)	200	100
Reference treatment	Placebo	None
Start of treatment	<24 h	<12 h
Start of treatment	7 h (mean)	5 h (mean)
Duration of treatment	14 days	7 days
Total number of patients	5778	16027
Outcomes		
Myocardial infarction*		
Beta blocker	70% (2028/2877)	59% (4672/8037)
Reference treatment	72% (2099/2901)	59% (4695/7990)
Rate ratio	0·97	0·99
95%-confidence interval	(0·94, 1·01)	(0·96, 1·02)
Mortality†		
Beta blocker	4·3% (123/2877)	3·9% (317/8037)
Reference treatment	4·9% (142/2901)	4·6% (367/7990)
Rate ratio	0·87	0·86
95%-confidence interval	(0·69, 1·11)	(0·74, 0·99)

Percentages are observed rates, with tallies in brackets.
* Myocardial infarction enzymatically or electrocardiographically (MIAMI only) confirmed.
† All-cause mortality over treatment period (14 days for MIAMI, 7 days for ISIS-1) on intention-to-treat basis.

salicylic acid in patients with confirmed unstable angina after stabilization of symptoms. Lewis and co-workers entered 1266 men with either new onset angina of effort, worsening angina of effort, or angina at rest who had experienced an episode of unstable angina in the week preceding hospital admission, provided that some evidence of coronary atherosclerosis was present[14]. Patients were screened within 48 hours after hospital admission and were randomised when a second electrocardiogram obtained after three hours confirmed the diagnosis of unstable angina. No further information on the delay between relief of symptoms and start of trial medication was provided. The trial regimen consisted of 325 mg of buffered acetyl salicylic acid daily or placebo. The most important finding was a decrease to one half of the incidence of acute myocardial infarction or death at twelve weeks. There was a (retrospectively) segregated group of patients (36 patients in each trial medication group) who had acute myocardial infarction at entry as evidenced from raised values for MB-creatine kinase within 12 hours of randomisation. These patients are not included in the tallies.

Cairns *et al.* entered 555 patients (75% men and 25% women) who appeared clinically to have unstable angina[15]. An unstable pain pattern (crescendo pain or pain at rest) and evidence for myocardial ischaemia (either from a Rose questionnaire for exertional angina, transient ST-segment or T-wave abnormalities during chest pain, or relief by glyceryl trinitrate in less than ten minutes on three or more occasions in the hospital) were required for eligibility, as was the absence of evidence for acute myocardial infarction in the preceding twelve weeks. The presence of evolving myocardial infarction was ruled out. The deadline for entry was eight days after admission to the coronary care unit. The drug regimens were double placebo, acetyl salicylic acid (1300 mg per 24 h) and sulfinpyrazone placebo, sulfinpyrazone (800 mg per 24 h) and acetyl salicylic acid placebo, or the combination of both drugs. No benefit for sulfinpyrazone was observed. As there is little evidence that sulfinpyrazone has a cardio-

Table 8.5 Summary of two placebo-controlled trials of acetyl salicylic acid in confirmed unstable angina after stabilization of symptoms

	Trial	
	Lewis[14]	Cairns[15]
Design features		
Year of publication	1984	1985
Index treatment	ASA	ASA*
Dosage (mg per 24 hours)	324	1300
Reference treatment	Placebo	Placebo
Start of treatment†	< 7 days	< 8 days
mean	unknown	unknown
Follow-up	12 weeks	18 months
Total number of patients	1266	555
Outcomes		
Failure of treatment‡		
ASA	5% (31/625)	12% (33/276)
Placebo	10% (65/641)	15% (42/279)
Rate ratio	0·49	0·79
95%-confidence interval	(0·32, 0·74)	(0·52, 1·21)
Mortality		
ASA	1·6% (10/625)	5·8% (16/276)
Placebo	3·3% (21/641)	10·0% (28/279)
Rate ratio	0·49	0·58
95%-confidence interval	(0·23, 1·01)	(0·32, 1·03)

ASA, acetyl salicylic acid.
Percentages are observed rates, with tallies in brackets.
* The Cairns trial also included treatment with sulfinpyrazone; these tallies only take account of the aspirin treatment.
† In reference to the last episode of chest pain.
‡ Death from whatever cause or the development of acute myocardial infarction.
§ All-cause mortality on intention-to-treat basis.
Unstable angina: Angina of new onset, worsening angina, or angina at rest in combination with other evidence of atherosclerotic coronary disease, in the absence of baseline evidence of acute myocardial infarction (see also text).

vascular effect, we have pooled the results of the sulfinpyrazone and the placebo arms. Rates for myocardial infarction or death (intention-to-treat) over an average follow-up period of 18 months were 12% under acetyl salicylic acid in comparison to 15% under placebo, a rate ratio of 0·77. The rate ratio for all cause mortality was 0·58. There were no differences in recurrence of unstable angina necessitating hospital admission or in indications for bypass surgery.

Findings from further trials in unstable angina

In 1982 Gerstenblith and co-workers reported a placebo-controlled randomised trial designed to assess the effect of nifedipine (40 to 80 mg per 24 h) when added in a randomised double-blind fashion to a standard regimen of propranolol (160 mg per 24 h) and nitrates (40 mg per 24 h) in patients with unstable angina at rest[16]. A later trial from the same institution did exactly the opposite. Gottlieb and co-workers randomised patients who all had been treated with nifedipine (80 mg per 24 h) and nitrates (40 mg per 24 h) to either additional propranolol (at least 160 mg per 24 h) or placebo[17]. In both trials patients admitted to hospital with a diagnosis of unstable angina, characterized by chest pain at rest with transient changes on the electrocardiogram were randomised after enzyme concentrations had remained below twice the normal level within 24 hours beforehand. It was not required for patients to remain pain free over these 24 hours. 'Failure of treatment' was defined as sudden death, myocardial infarction, or persistent angina requiring surgery or angioplasty during the four (Gerstenblith) or one (Gottlieb) month follow-up period. Rates of treat-

ment failure in the Gerstenblith trial were 44% (30/68) under nifedipine and 61% (43/70) under placebo, a rate ratio of 0·72; 95%-confidence interval: (0·51, 0·99). The difference was mainly due to persistent chest pain requiring surgery (18/68 under nifedipine versus 29/70 under placebo). Rates of treatment failure in the Gottlieb trial were 38% (16/42) for propranolol and 46% (18/39) for placebo, a rate ratio of 0·83; 95%-confidence interval: (0·49, 1·38). Most (74%) of these failures consisted of an indication for surgery or angioplasty.

In 1981 Telford and Wilson reported findings of a randomised, double-blind, placebo controlled trial of heparin, atenolol, and their combination in the prevention of myocardial infarction in patients with the 'intermediate coronary syndrome'[18]. Four hundred patients with either accelerating angina of effort, angina at rest, or 'subendocardial' infarction were enrolled. No indication was given when treatment was started in reference to onset of the presenting symptoms. Of the randomised patients 186 were withdrawn from the analysis: 51 did not satisfy the entry criteria; 84 were incorrectly diagnosed as cardiac pain; 43 had unrecognized acute 'transmural' myocardial infarction which had already occurred before admission; and 8 were psychologically unsuitable. The main outcome event was the occurrence of 'transmural' infarction within the treatment period of seven days. The rates were 17% (9/54) for placebo, 13% (8/60) for atenolol; 2% (1/51) for heparin; 4% (2/49) for the combination. The rate ratio for heparin (disregarding atenolol) was 0·20; 95%-confidence interval: (0·06, 0·62).

Discussion

The fate of a patient with prolonged anginal pain at rest may be cast away during the first few hours. Treatment may affect early fatal complications and progression to myocardial infarction in those who survive initially. Trials in acute patients are therefore extremely important. Given the rapidly changing symptoms and signs in the early hours they are difficult to design so as to allow clear-cut generalization of results to indications which can be recognized in clinical practice. Most of the unstable angina trials, unfortunately, mix aspects of early treatment (cooling off) with secondary preventive measures. Generalization of many of these trials is therefore problematic.

As regards the indication studied in the Muller unstable angina trial, the report does not explicitly mention whether known normal enzyme values were required for eligibility or not. In addition there was no placebo reference group and interpretation depends on the way one rates conventional treatment. These features hamper generalization. The data of this trial indicate that in patients not on previous maintenance treatment with a beta blocker treatment with nitrates and propranolol may eliminate episodes of recurrent chest more rapidly and more thoroughly than nifedipine may do. The data also indicate that in patients on maintenance treatment with a beta blocker the addition of nifedipine may control chest pain more rapidly than treatment with nitrates and additional beta blockers may do. This dependency of nifedipine's efficacy in achieving control of chest pain on the presence of previous treatment with a beta blocker was similar to that observed in HINT.

The findings of TRENT provide substantial evidence that nifedipine is of no benefit in the prevention of early death in suspected acute myocardial infarction. The other three nifedipine trials in suspected acute myocardial infarction support this finding. In addition, they provide some indication that nifedipine neither influences eventual myocardial infarction nor limits infarct size. The width of confidence limits of the Branagan study clearly indicates that such a small study is actually noninformative.

The role of other calcium-antagonists in suspected acute myocardial is not yet defined. Calcium antagonists are far from homogeneous and what applies to nifedipine may not apply to verapamil or diltiazem. In this context, however, the findings of the Danish verapamil study must be mentioned[19]. In this randomised placebo-controlled trial treatment with verapamil or placebo was started at hospital admission in all patients suspected of possibly having acute myocardial infarction, provided that they were not on a beta blocker or a calcium antagonist already. However, treatment was continued for six months only if infarction was confirmed; if this was not the case (in 60% of patients), study treatment was discontinued as soon as the diagnosis became clear. Thus the design mixes aspects from acute intervention and secondary prevention trials in such a way that it cannot be considered as internally valid for either indication. Generalization of the, otherwise unpromising, results is virtually impossible.

The diltiazem trial reported by Gibson entered in patients with non-Q-wave infarction[20]. Entry must therefore have taken place at least 24 hours after onset of infarction. Notwithstanding its relatively short follow-up (14 days), this trial thus belongs to the category of secondary prevention trials after

confirmed myocardial infarction and was hence not discussed herein.

The role of beta blockers in suspected acute myocardial infarction has been delineated by the MIAMI and ISIS-1 trials. The observed treatment effects in these trials, together with their 95%-confidence intervals, provide strong evidence that these beta blockers have a positive, albeit modest, effect on early mortality in the low risk subgroup of patients with suspected acute myocardial infarction in a suitable haemodynamic condition. Lowering mortality should not be the only reason for beta blockade as supportive treatment in this condition. Other modest beneficial effects were observed in MIAMI, such as a reduced need for opiates, anti-arrhythmic drugs, and cardiac glycosides[10]. Safety of beta blockers in this indication appears not to be an issue, as long as one takes account of contra-indications. It has been argued that it must be regretted that clinical usefulness of the drugs was in neither study evaluated by comparing the percentages of patients without any complications during hospital stay[21].

The two trials provide evidence for metoprolol and atenolol in the first place. Whether this effect on early mortality may also be expected with other beta blocking agents is a matter of judgment, based on pharmacologic insight, maybe in combination with results of other trials in (late) myocardial infarction.

Importantly, patients already on beta blockade were excluded. As a result, a withdrawal effect cannot be the explanation. Otherwise, it is obvious that the treatment effects observed in both studies were modest and that very large numbers were required to estimate the effect sufficiently precisely. This was to be expected: by excluding patients with signs of cardiac failure the high risk patients are eliminated and one is left with a group of patients with a low mortality within the safe confinement of a coronary care untit, where complications such as ventricular fibrillation need not be fatal.

An effect of beta blockade on early mortality would gain credibility if there was a clear explanation for mechanism. Trials are not done to elucidate mechanisms of action but the data may provide some clues. Prevention of ventricular fibrillation cannot be the only explanation because the effects on its incidence were very modest in both MIAMI and ISIS-1. Infarct size limitation may show up in trials like these as a difference between the percentages of eventually confirmed myocardial infarction. In MIAMI such differences were observed only for patients treated early (within 7 hours from onset). Evidence from earlier studies on beta blockade and infarct size have been conflicting. Examination of the data of (small) trials in which infarct size was measured indicate that a moderate effect on enzyme levels may be expected from early intravenous beta blockade[8]. These studies however showed conflicting results, most likely at least in part due to the fact the patients were entered with different delays after onset of symptoms. Also, theoretical doubts in regard infarct size limitation by beta blockers have been raised[22].

Threatened infarction was defined as the occurrence of characteristic chest pain suggestive of acute myocardial infarction but (as yet) without diagnostic electrocardiographic changes. It is thus a subcategory of 'suspected acute myocardial infarction' and is distinct from suspected unstable angina. The trials by Norris and Yusuf are infarction trials in the first place. Both present specific problems of interpretation. In the Norris trial, the placebo rate for eventual infarction, and consequently the rate ratio, is rather extreme and does not accord with other trials. We hypothesize, in retrospect, that chance may have inflated the observed treatment effect in a small trial like this, which may have led to '*P*-value biased' publication. The Yusuf trial raises doubts about its internal validity. The unequal distribution of threatened infarction over the overall treatment groups together with the reported irregularities in the randomisation procedure with the (in itself unreliable) envelope method suggests that physicians have been able to manipulate treatment assignment.

The evidence provided by the two acetyl salicylic acid trials in unstable angina is very convincing within the context of the two trials themselves. The Cairns trial may, in all probability, be taken as having included patients with confirmed unstable angina after stabilization of symptoms. Therefore its findings can be generalized to a recognizable clinical indication: secondary preventive measures in unstable angina after stabilization of symptoms. The Lewis trial, by contrast, has included a mixture of patients with stabilized symptoms and those in the midst of clinical instability: patients were entered within 51 hours of admission to hospital until seven days after an episode of unstable angina; but also patients who had, in retrospect, acute myocardial infarction at entry were entered. The fact that a mixture of different categories of patients was included does not imply that the findings may therefore be generalized to both indications. No information was provided as to how many patients were in stable condition and how many were still unstable. So it remains speculative as to whether the indication pertains to 'cooling of' unstable angina or to secondary

prevention in patients with a recent history of unstable angina. We have speculated that most patients were already in stable clinical condition upon entry and have therefore grouped the Lewis trial under this heading. (With this in mind, we also considered it to be justifiable to omit the segregated group of patients with infarction around entry from the intention-to-treat analysis.)

Generalization from the Gerstenblith and the Gottlieb study is difficult. It is not entirely clear which indication was studied. In both studies the absence of myocardial infarction was confirmed on the basis of enzyme assays. But were the patients in both studies still experiencing episodes of chest pain at the moment of randomisation. Or had symptoms been stabilized? If they were still experiencing anginal attacks while on the standard treatment regimen, they must be considered refractory to the respective standard treatment regimens, in which case they were therapeutic failures (of propranolol and nitrates in the first study and of nifedipine and nitrates in the second study) and qualitative interactions must be expected. Indeed, both studies observed a favorable effect of the addition of nifedipine in the first study and of propranolol in the second. Although the indication for additional treatment would be clear as such in both instances, the effects would not be generalizable outside the specific context in which they were observed. If patients were, on the other hand, in a stable condition at randomisation, the indication would amount to secondary prevention in patients with a recent history of unstable angina. Again would the indication be clear as such, although different in nature. A different generalization would consequently result but again would have to remain strictly within the context of the specific context studied. If the admitted patients would constitute a mix of both types of patients, generalization becomes virtually impossible. Combination studies as the latter two can, generally speaking, not be generalized to effects of mono-treatment as first choice treatment. However, they may provide important guidelines for what to do in clinical practice if (established) standard treatment fails and other measures must be considered.

The trial by Telford and Wilson included patients in different phases of unstable angina and evolving myocardial infarction, which was not further specified. Furthermore, almost 50% of randomised patients were excluded from the analysis, and not only for unequivocal violations of the admission protocol. Therefore, generalization of this small, internally invalid study is doubtful. As a matter of fact, the results by themselves also raise questions—for heparin virtually eliminated myocardial infarction. The rate ratio for heparin in this small study was 0·2·, which seems too much of the good.

Although we did not explicitly review trials of coronary bypass surgery in unstable angina, it is important to mention how they fit into the scheme of Table 8.1. The National Cooperative Unstable Angina Pectoris Trial was designed to compare pharmacologic treatment with coronary bypass surgery in unstable angina patients after an observation period of 24 hours after relief of pain, without enzyme rises[23]. Surgery was performed after 8 days on the average. Other trials, also performed in the seventies, had similar selection procedures[24]. These trials thus pertain to the indication 'confirmed unstable angina after stabilization of symptoms'. It was widely accepted that the data of these trials indicated that urgent surgical treatment after an interval of 24 hours had no advantage over urgent pharmacologic treatment in terms of early mortality;[25]. As regards angioplasty, no randomised studies have yet been performed.

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9 General discussion

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Introduction

In chapter 5 we have put forward that the primary task of investigators is to summarize the evidence obtained from a clinical trial and that conclusions (i.e. incorporation of the findings into the existing body of scientific knowledge) should be left to the medical community at large. It is customary that investigators also present their personal conclusions and we will do so likewise.

This discussion consists of some general remarks on methodological aspects of the design of HINT and its execution, to be followed by an estimation of the frequency by which unstable angina is seen at admission to the coronary care unit and we will provide a description of its short-term clinical course. Furthermore, trial medication effects as observed in HINT are related to findings of other trials, and a management strategy for unstable angina is proposed. Finally, some of the new developments in the treatment of unstable angina and possibilities for further clinical research are outlined.

Methodological aspects

A violation of the admission protocol occurred in 131 patients. Because these patients did not have unstable angina as defined by the HINT protocol, we excluded them from the analysis (see discussion chapter 3). Another 22 patients with pre-randomisation myocardial infarction were no longer at risk of the defined outcome events, and these patients were also excluded from trial medication effect assessment (see discussion chapter 4). We believe this to be the correct procedure. To allow for effect analyses based on other principles, tallies in which these patients were included have also been provided (Tables 4.9 and 7.1).

We have chosen to quantify treatment effects as rate ratios and to express the inherent uncertainty in these effect estimates by the corresponding 95%-confidence intervals. This provides a better indication of the magnitude of the expected therapeutic benefit and of the statistical strength of the evidence rather than the customary significance levels (*P* values) do. We feel that they should be used in all reporting of clinical trials.

Although the total number of patients entered in HINT is large, the treatment groups by themselves are rather small. In a randomised trial with small groups differences between the groups in baseline risk may occur due to random variation. Table 5.6 indicates that this indeed was the case. This observation does not imply that our procedure of treatment allocation was faulty; it can be calculated that an imbalance of at least this size may occur in about 16% of similar, truly random allocations. We used risk stratification based on a composite logistic function of influential baseline characteristics and have expressed trial medication effects as ratios of weighted averages of stratum specific rates, an approach which ensures that the estimation of trial medication effect becomes independent of the actual distribution of baseline risk in the groups that are compared. It must be noted, however, that the composition of the function to estimate baseline risk requires judgment on the part of the investigator; the procedure thus contains an element of subjectivity. Those readers who reject the underlying principles should base their inference on unadjusted effect estimates, which have also been provided (Table 5.1).

An important feature of HINT was its early termination upon a recommendation by the Policy Advisory Board. The decision as such is beyond dispute in this context. Even in retrospect, we regard it very unlikely that other decisions with regard to nifedipine monotherapy would have been taken, had the final effect estimates been available at that time. From the efficacy assessment point of view, the distinction between 'no effect' and a 'detrimental effect' is moot. From the ethical point of view, it is unjustifiable to continue a trial in spite of a negative trend until the distinction between 'no effect' and 'detrimental effect' can be established beyond reasonable doubt. As far as the other treatments are concerned, other decisions, however, might have been taken in the presence of a more detailed analysis. It goes without saying that data management must be organized in such a way that a full analysis can be carried out at short notice and that decisions on data analytic procedures should be taken before the issue of possible termination arises.

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Occurrence and clinical course of unstable angina

HINT aimed to select a group of patients with episodes of prolonged anginal pain at rest, either observed or by history. This diagnosis of unstable angina at rest (a subcategory of unstable angina) was based upon a combination of findings—prolonged chest pain at rest, evidence for myocardial ischaemia, and absence of signs of acute myocardial infarction (chapter 3). Eligibility for HINT represents a distinct clinical entity (and hence a potential indication for treatment) clearly recognised at admission to hospital: symptoms and signs indicating acute but still reversible myocardial ischaemia.

Because of the provisional and changing nature of the admission diagnosis (see chapter 1) it is difficult to collect data which depict the frequency by which the syndrome of unstable angina as defined in HINT is encountered among patients currently admitted to the coronary care unit. This frequency probably depends on the extent to which a particular clinic acts as a secondary referral centre, on the threshold for patients coming to the emergency room, on the delay times involved, etc. Figures on discharge diagnoses of all admissions to the coronary care unit are available for one participating department. In 1986, 1150 patients were admitted to the coronary care unit of the Thoraxcentre, the referral centre in the Rotterdam area. The 56 cases with angina at rest among 250 secondary referrals (i.e. patients referred from other hospitals) represented in virtually all instances failure of previous intensive pharmacologic treatment. Hence the HINT findings do not bear on them. Of the remaining 900 patients (primary admissions) 101 had a *discharge* diagnosis of 'angina at rest'. Patients who developed myocardial infarction but who initially presented with symptoms and signs of unstable angina are not counted in this category. Based on our prospective HINT data, this applies to 20–25% of patients with 'angina at rest' at hospital admission. This would lead to an estimated 135 patients with the *admission* diagnosis 'angina at rest'. Allowing for the fact that an admission diagnosis of 'angina at rest' may eventually be revised into 'atypical chest pain' or 'crescendo angina', we estimate that each year approximately 150 patients are admitted with angina at rest to the Thoraxcentre. Of these patients, approximately 50% appears to be on maintenance treatment with a calcium antagonist, which leaves 75 patients to whom the research issue investigated in HINT is relevant. Thus in this hospital, the syndrome represented by the HINT patients pertains to approximately 8% of all current primary admissions to the coronary care unit.

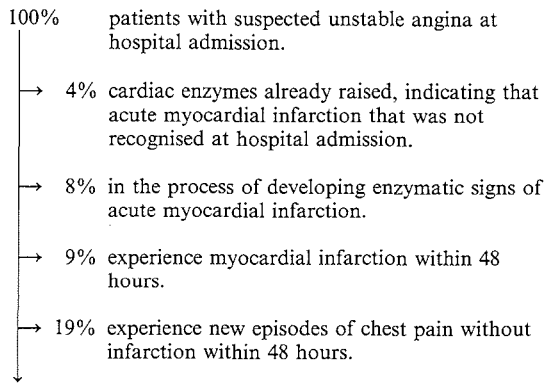

Figure 9.1 Short-term clinical course of patients admitted to the coronary care unit with symptoms and signs indicating unstable angina.

It is generally recognised that the differentiation between unstable angina and acute myocardial infarction at hospital admission is difficult. The short-term clinical course of these patients, based on the HINT data, is summarized in Fig. 9.1.

The risk profile of these patients (Table 5.5) indicates that there is considerable variation in risk. Broadly speaking, two categories of patients can be discerned: (1) those with chest pain persisting until after hospital admission, accompanied by ST-segment changes in the electrocardiogram (high risk patients); and (2) those whose chest pain had subsided spontaneously before admission to hospital and who have an almost normal electrocardiogram (low risk patients). On the basis of a few baseline characteristics substantial differences in clinical course can be predicted, e.g. a 75% risk for recurrent ischaemia or myocardial infarction within 48 hours in typical high risk patients versus 25% in typical low risk patients.

This finding may have important clinical implications. In high risk patients stabilization of symptoms with pharmacologic treatment seems unlikely. This may constitute a point to schedule angiography early, without waiting for symptoms to recur. Further treatment would then be guided by the physician's knowledge of the coronary anatomy. On the other hand, low risk patients can be admitted to a 'medium care unit', and a wait-and-see policy as far as angiography is concerned may be considered.

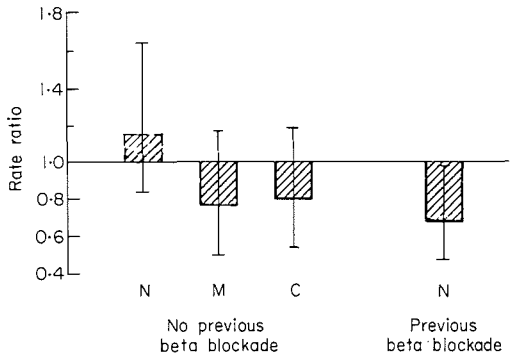

Figure 9.2 Rate ratios of recurrent ischaemia or myocardial infarction within 48 hours (with 95%-confidence intervals) for all comparisons of active trial medication with corresponding placebo. For instance, the rate ratio for metoprolol is the rate of recurrent ischaemia or myocardial infarction within 48 hours in the metoprolol group divided by that in the placebo group (among patients not on previous maintenance treatment with a beta blocker). Thus a rate ratio of 1 indicates that metoprolol has no effect. A rate ratio of < 1 points to a preventive effect and a rate ratio of > 1 to a negative effect. These rate ratios have been adjusted for incomparability of baseline risk (chapter 5) (N—nifedipine, M—metoprolol, C—combination).

Commentary on observed trial medication effects

Estimated trial medication effects (the rate ratios from Table 5.7) are depicted in Fig. 9.2. Of the trial medications studied, the addition of nifedipine to previous maintenance treatment with a beta blocker was clearly beneficial. None of the other treatment effects came out unequivocally effective, but the data indicated that treatment with metoprolol may exert a beneficial short-term effect in patients not on previous maintenance treatment with a beta blocker. Furthermore, the fixed combination of metoprolol with nifedipine would not provide any further gain. (The rate ratio of the combination relative to metoprolol alone was 1·06, 95%-confidence interval: (0·67, 1·70).) On the other hand, the data also indicated that one may not expect therapeutic benefit from nifedipine monotherapy when given to patients that were not on previous maintenance treatment with a beta blocker. In particular, there was a worrisome trend towards an increased risk for myocardial infarction for nifedipine alone: a rate ratio of 1·51, 95%-confidence interval: (0·87, 2·74).

These findings fit a pattern of results observed in other trials, which have been described in chapter eight. Only one of these (by Muller and co-workers) explicitly addressed the indication 'unstable angina' as admission diagnosis[1]. The effect of nifedipine was compared to that of conventional treatment with beta blockers and nitrates, and it was also observed that nifedipine's efficacy in achieving control of chest pain largely depended on the presence of previous maintenance treatment with a beta blocker: if present, nifedipine was efficacious; if not, nifedipine seemed to promote recurrence of chest pain. Thus, two independent clinical trials have provided evidence for the existence of a qualitative interaction of nifedipine and previous beta blockade as far as efficacy in preventing recurrent chest pain or progression to myocardial infarction is concerned.

What could be the explanation for this finding? It could be that in patients whose condition has become unstable in spite of maintenance treatment with a beta blocker, increased vasomotor tone or coronary spasm plays a larger role than it does in patients not on previous beta blockade. This would explain the efficacy of additional treatment with a coronary spasmolytic agent as nifedipine. Another possibility would be that a potential harmful reflex tachycardia, which may be induced by nifedipine, is offset by previous or concomitant use of a beta blocker.

The comparison of nifedipine monotherapy with placebo (among patients not on previous beta blockade) virtually excludes a major preventive effect of nifedipine used in this way for this indication. This accords with findings from four recent trials, which all indicated that no therapeutic benefit may be expected of nifedipine when given to patients with suspected acute myocardial infarction (see chapter 8). It must be emphasised that animal experiments already indicated that no protective effect may be expected from nifedipine when given after onset of ischaemia[2].

Nifedipine was originally recommended to be of particular value of patients with ST-segment elevation in the electrocardiogram, which may reflect transmural myocardial ischaemia due to coronary spasm[3]. These patients, however, did not seem to benefit particularly from nifedipine treatment (Tables 5.10a and 5.10b). It is noted, however, that these effect estimates lack precision.

It has been suggested that a beta blocker might be contra-indicated in patients with unstable angina because it might induce coronary spasm in some patients[4]. The findings of HINT indicate that this alleged effect is not an important therapeutic consideration. By itself the evidence from HINT for a salutary effect of treatment with metoprolol (among patients not on previous maintenance treatment with

a beta blocker) was not conclusive; the 95%-confidence interval was rather wide. The rationale for a beta blocker such as metoprolol as 'first choice' in this indication must therefore be based in part on their established efficacy in suspected acute myocardial infarction (see chapter 8). Taken together, these findings point towards a wide range of indications, varying from symptoms and signs typical for unstable angina (reversible ischaemia) to those typical for uncomplicated acute myocardial infarction (limited necrosis), in which beta blockers such as metoprolol or atenolol can be expected to provide a modest therapeutic benefit.

Some authors have recommended that patients with unstable angina at rest be immediately treated with a combination of a nitrate, a beta blocker, and a calcium antagonist[5]. The data of HINT do not support this recommendation as far as the combination of metoprolol and nifedipine is concerned: this combination appeared not to provide greater therapeutic benefit than that provided by metoprolol alone.

In summary, a beta blocker such as metoprolol must be considered an important therapeutic option in the initial pharmacotherapeutic approach to unstable angina. On the other hand, a calcium antagonist such as nifedipine, either as monotherapy or in combination with a beta-blocker, does not appear to be a first therapeutic option. Nifedipine, however, seems to be a useful addition to the therapeutic regimen when initial treatment with a beta blocker has failed.

Proposed management strategy

Today, the *initial* therapeutic approach in the management of unstable angina is pharmacologic, as it was in 1980 when HINT was designed. The therapeutic objective is to stabilize the symptoms and to prevent progression to myocardial infarction. As a consequence, the treatment effects observed in HINT are relevant for the initial management of patients with unstable angina admitted to the coronary care unit in 1987.

What follows is a proposed management strategy. It may be viewed as an update of the scheme provided in Table 1.2, in which our conclusions from HINT have been incorporated. It is noted that this scheme contains many elements which are, of necessity, based on theoretical arguments supported by clinical experience rather than on results of HINT or other randomised clinical trials.

The first consideration in the management of patients coming to the hospital with symptoms and signs indicating unstable angina would be to distinguish between high and low risk patients. The typical high risk patient has chest pain when arriving at the hospital and has at least 0·1 mV ST-segment displacement (and even more during chest pain) in the electrocardiogram. Admission to the coronary care unit seems warranted. Angiography may be scheduled at an early convenience. Intensive pharmacologic treatment starts with a combination of beta blockers, intravenous glyceryl trinitrate, and heparin. A calcium antagonist is included in the above regimen only if a beta blocker was already being taken when unstable angina developed. If a beta blocker is contraindicated, one may consider to substitute a calcium antagonist in the above regimen, the choice of which is, at present, primarily guided by pharmacologic properties. If pharmacologic treatment of this sort fails, immediate angiography is performed and, depending on the findings, angioplasty or bypass surgery can be carried out[6]. If pharmacologic treatment is successful, (semi)elective angiography is indicated, and angioplasty or bypass surgery may be carried out, depending on the angiographic findings. Long-term preventive treatment may include platelet aggregation inhibiting drugs or a beta blocker.

The typical low risk patient arrives at the hospital after spontaneous relief of chest pain at home and appears to have an almost normal electrocardiogram, or at least no substantial ST-segment displacements. This patient need not necessarily be admitted to the coronary care unit. Initial treatment with a beta blocker, or with an additional calcium antagonist when beta blockers were already being taken, suffices. If chest pain recurs (with accompanying ST-segment displacements on the electrocardiogram), the patient becomes a 'high risk' patient and subsequent management develops as described above. If chest pain does not recur, or if no ST-segment changes are observed during chest pain, exercise testing and/or 24 hours ambulatory electrocardiography is performed to identify which patients should be further evaluated by angiography.

It is noted that not all patients present with a clinical picture as clear-cut as above as far as risk stratification is concerned. The treating physician's subjective assessment of risk may be then the deciding factor in the treatment choice.

New developments

As stated in the discussion of chapter 4, the timing of the onset of infarction in HINT patients indicated that treatment which aims at the prevention of pro-

gression to myocardial infarction will have a limited effect because in most cases it will come too late. Therefore, thrombolytic treatment, either with intracoronary or intravenous streptokinase or with intravenous recombinant tissue-type plasminogen activator, must be considered a therapeutic option worthy of further investigation, in particular in high risk unstable angina patients whose symptoms have occurred within the last few hours. Of the HINT patients, 21% (22 + 92 out of 537 patients) developed signs of acute myocardial infarction within 48 hours. Of these infarctions, infarct size might have been limited in those with an onset before randomisation, whereas some infarctions with an onset after randomisation may even have been prevented altogether by thrombolytic treatment. Furthermore, thrombolytic treatment may also prevent recurrence of symptoms[7]. On the other hand, the risks of thrombolytic treatment (in particular for a rare cerebro-vascular accident) must have greater weight in unstable angina than in acute myocardial infarction. In this context it is important to note that most of the HINT infarcts were enzymatically rather small (Table 4.4). Of course, the balance of expected therapeutic benefit against risks will change considerably if one were to consider high risk patients only.

The assessment of the efficacy of intravenous thrombolytic treatment will be an important target for future clinical research in unstable angina. One may consider clinical trials in which the efficacy of intravenous thrombolytic treatment is compared with that of conventional treatment.

New developments which arise from the above arguments (as collected from a recent review of current concepts and management[8]) need be evaluated in clinical trials with a design similar to that of HINT. The problems of carrying out a randomised trial in this indication in such a way that its findings have real clinical significance are compounded by the fact that clinical management of this syndrome involves a chain of decisions to be taken at various stages of the disease, which sometimes follow one and another within hours. HINT was a trial in which only one step in this process (the decision on the initial use of a beta blocker, a calcium antagonist, or their combination) was assessed. Hence it provided only information on the initial choice between these agents. An alternative approach would be to compare overall management strategies by clinical trial, e.g. a conservative approach (for instance beta blockade only and late angiography) versus an aggressive approach (full medication and early angiography/angioplasty/surgery). Efficacy in such a comparison can be measured by the total number of infarcts eventually diagnosed in, for instance, the first two weeks. Consequently, such a trial would be much easier to carry out—for the complication of determining (in an unbiased way) whether recurrent ischaemia has occurred is avoided. On the other hand, more patients have to be enrolled. Furthermore, one might consider to perform such a trial in high risk patients only. The entry criteria would be more simple (e.g. in-hospital chest pain with at least 0·1 mV ST-segment displacement on the electrocardiogram, in the absence of symptoms and signs of acute myocardial infarction). An other 'advantage' would be a higher infarct rate so that treatment effects on this outcome can be measured with greater precision. This statement does not imply that management of the low risk patient is unimportant per se; the research questions involved are, however, at present less well suited for clinical research.

Further unresolved questions regarding the treatment of unstable angina pectoris include the relative efficacy of angioplasty and bypass surgery in the treatment of refractory angina. Also, elimination of silent ischaemia has been suggested as an important approach in the long-term management of unstable angina[9]. Further work is needed to define comparative efficacy of various drugs in reducing asymptomatic and symptomatic episodes of myocardial ischaemia and its relation to an improvement in mortality and morbidity in patients with unstable angina[10].

Whatever treatment or management strategy is under study, the distinction between early management and late long-term preventive treatment should be appreciated in the design of future trials. A further important aspect is to distinguish between efficacy of a certain drug in hitherto untreated patients and efficacy of the same drug in patients who already have failed one or more previous (standard) treatments. The HINT findings exemplify the by itself plausible notion that a positive effect of additional treatment with a certain drug (after failure of standard treatment) cannot necessarily be generalized to a positive effect of the same drug when given alone, as 'first choice' treatment. It follows from this that the interpretation of trials which have included an unspecified mixture of both types of patients will remain unclear.

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Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both

REPORT OF THE HOLLAND INTERUNIVERSITY NIFEDIPINE/METOPROLOL TRIAL (HINT) RESEARCH GROUP

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Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both

*REPORT OF THE HOLLAND INTERUNIVERSITY NIFEDIPINE/METOPROLOL TRIAL (HINT) RESEARCH GROUP†

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SUMMARY A multicentre, double blind, placebo controlled, randomised trial of nifedipine, metoprolol, and nifedipine and metoprolol combined was conducted in a group of 338 patients with unstable angina not pretreated with a β blocker and of nifedipine in 177 patients pretreated with a β blocker. The main outcome event was recurrent ischaemia or myocardial infarction within 48 hours. Trial medication effects were expressed as ratios of event rates relative to placebo. In patients not pretreated with a β blocker the event rate ratios with associated 95% confidence intervals were 1·15 (0·83, 1·64) for nifedipine, 0·76 (0·49, 1·16) for metoprolol, and 0·80 (0·53, 1·19) for nifedipine and metoprolol combined. In patients already on a β blocker the addition of nifedipine was beneficial (rate ratio 0·68 (0·47, 0·97)). Equal numbers of patients developed myocardial infarction and reversible ischaemia. Most infarctions occurred early, within six hours of randomisation. In patients not already on a β blocker the nifedipine rate ratio for infarction only was 1·51 (0·87, 2·74).

These results suggest that in patients not on previous β blockade metoprolol has a beneficial short term effect on unstable angina, that fixed combination with nifedipine provides no further gain, and that nifedipine may be detrimental. On the other hand, the addition of nifedipine to existing β blockade when the patient's condition becomes unstable seems beneficial.

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Patients admitted to a coronary care unit with acute chest pain present a spectrum of signs and symptoms ranging from those that are characteristic of acute myocardial infarction to chest pain without myocardial ischaemia. Within these two extremes a subgroup of patients can be identified who have signs and symptoms that are atypical of myocardial

infarction but characteristic of myocardial ischaemia—anginal pain at rest not severe enough to suggest myocardial infarction, combined with changing electrocardiographic findings compatible with ischaemia but not directly diagnostic of infarction. This syndrome is usually called unstable angina. Patients with this diagnosis at admission to the coronary care unit may be in the process of sustaining a myocardial infarction. Alternatively, the infarction may not yet have occurred, and the patient should be considered at risk for recurrent and possibly irreversible ischaemia.[1-3]

After initial pain relief the aims of early treatment are the prevention of recurrent ischaemia or myocardial infarction and the restoration of a stable condition. Calcium antagonists and β blockers are among the agents that have been advocated as being useful in this respect.[4-8] Calcium antagonists are thought to increase oxygen supply by coronary vasodilation and β blockers are assumed to reduce oxygen demand by decreasing heart rate and myocardial contractility.[9 10] However, β blockers have also been implicated as a potential cause of increased coronary vasomotor tone[11 12] and calcium antagonists in the coronary steal phenomenon.[9 13] Furthermore, several cases of severe congestive heart failure have been reported in patients treated with both drugs.[14 15]

In 1980 the Holland Interuniversity Nifedipine/metoprolol Trial (HINT) research group initiated a randomised, double blind, placebo controlled, multicentre trial to assess the role of calcium antagonists and β blockers in the treatment of unstable angina. At that time this role had not been defined.[16] The objective of the trial was to determine whether nifedipine (a calcium antagonist) and metoprolol (a β blocker) could prevent recurrence of ischaemia or progression to myocardial infarction when given either alone or in combination to patients diagnosed as having unstable angina at admission to the coronary care unit. The trial was confined primarily to an observation period of 48 hours, although long term follow up continues. The protocol was designed to follow established cardiological practice as closely as possible. In particular, patients were admitted to the trial as soon as unstable angina was suspected before myocardial infarction could be excluded by enzyme measurements.

The trial was carried out under the auspices of the Interuniversity Cardiology Institute, in which all academic cardiology departments in the Netherlands participate. The trial was funded by the Dutch Ministry of Education. In addition, it was supported by grants from Bayer GmbH, Wuppertal, Germany, and Hässle AB, Mölndal, Sweden.

The first patient was enrolled on 1 February 1981. On 30 October 1984 enrolment was discontinued because an interim analysis suggested that the risk of myocardial infarction was higher in patients assigned to nifedipine than in patients treated with the other trial medications. The data on which this decision was based are reproduced in appendix I. Both Bayer and Hässle and the Dutch health authorities were informed of the decision but not of the actual data. This report deals with the main findings on the efficacy of nifedipine and metoprolol in preventing recurrent ischaemia and myocardial infarction in the 515 patients who were eventually available for analysis.

Patients and methods

ORGANISATION

Eight university and three non-university cardiology departments participated. Before the start of the trial the protocol was approved by the Scientific Council of the Interuniversity Cardiology Institute and by the principal investigators of participating non-university hospitals (together they formed the Executive Committee) and by the ethics committees at each participating centre. A Policy Advisory Board of acknowledged experts in related fields, not otherwise associated with the trial, also approved the protocol and adopted the task of progress monitoring. Until the decision was taken to discontinue the trial only this board was informed of the interim results.

Data were processed by the Clinical Epidemiology Unit of the Thoraxcentre in Rotterdam, which also provided overall coordination. Its staff was kept unaware of the patient medication assigned and interim results until the trial was discontinued.

The clinical course, electrocardiograms, and laboratory data of each patient up to 48 hours after start of trial medication were reviewed by a committee of three experienced cardiologists. This Classification Committee, which was unaware of the trial medication assignment and findings at subsequent angiography, determined which clinical events had taken place up to 48 hours after randomisation, according to predefined guidelines.

PATIENT RECRUITMENT AND INCLUSION CRITERIA

At admission to hospital patients were screened for immediate inclusion before the results of the enzyme measurements were known. Chest pain (if present) was treated with sublingual glyceryl trinitrate (maximum two 0·5 mg doses) and if it persisted an intravenous injection of glyceryl trinitrate (maximum 1 mg in 10 ml 5% glucose) or fentanyl (0·05 mg) was given.

To qualify for admission to the trial the presence of either of the following was required: a chest pain

episode in the hospital accompanied by a varying pattern of ST-T changes suggesting reversible myocardial ischaemia; a history of typical angina at rest or during light activity occurring within 12 hours of admission and lasting > 15 min combined with either ST-T abnormalities, a documented history of myocardial infarction or unstable angina, or at least 50% narrowing of a major coronary artery observed at earlier angiography. Patients who did not qualify at hospital admission were included on the basis of the above criteria when chest pain subsequently developed, provided that available enzyme values were below twice the local upper limit for normal.

If pain could not be relieved as described above, the patient was not admitted to the trial. In addition, the following exclusions were applied: age > 70, new Q wave formation on the electrocardiogram, acute myocardial infarction within one week, maintenance treatment with nifedipine, heart rate below 50 or above 120 beats/minute, systolic blood pressure < 100 mm Hg, systolic blood pressure > 170 mm Hg and diastolic pressure > 110 mm Hg, conduction abnormalities other than bundle branch block, anaemia (haemoglobin < 6·5 mmol/l, if known), clinically overt heart failure, congenital or valvar heart disease, cardiomyopathy, serious pulmonary or other non-cardiac disease, and previous participation in this trial. After eligibility had been established, oral informed consent was asked for and if it was obtained the trial medication was started without further delay.

TREATMENT

All patients received routine care for at least 48 hours. Sedatives and anticoagulants were given according to local practice. Oral long acting nitrates were continued if they had been given before admission to hospital; otherwise these drugs were not part of the standard regimen. Antiarrhythmics, digitalis, diuretics, and antihypertensive agents other than β blockers were given on indication only. Previous maintenance treatment with a β blocker was continued; before 13 November 1982 with the same compound and dose as given before, thereafter with two 100 mg doses of metoprolol per 24 hours. Chest pain was initially treated as described above. If pain persisted the decision to use further measures was left to the discretion of the attending physician.

Trial medication was added to the standard regimen as follows. Patients not on previous maintenance treatment with a β blocker for > 3 days were randomly assigned to receive either double placebo, nifedipine six 10 mg doses per 24 hours plus metoprolol placebo, metoprolol two 100 mg doses per 24 hours plus nifedipine placebo, or both drugs. Patients on previous maintenance treatment with a β blocker were randomly assigned to receive placebo or nifedipine six doses of 10 mg per 24 hours. No loading dosages were given. Both nifedipine and metoprolol (or their placebos) were started at the same time. Both randomisation procedures were performed for each clinic separately and in equal proportions.

Unless persistent chest pain developed, the trial medication was continued for at least 48 hours, preferably until catheterisation or discharge. In the event of suspected side effects trial medication was reduced or discontinued. The treatment code could be broken but only if it was considered mandatory by the attending physician. For this purpose a coding envelope was packed with each package of the trial medication.

DATA COLLECTION AND FOLLOW UP

Twelve lead electrocardiograms were recorded every six hours as well as during and after episodes of chest pain over the period from hospital admission until 48 hours after start of trial medication. The extent of ST depression and elevation was coded as described in appendix II in two electrocardiograms recorded before start of trial medication—that is, the last electrocardiogram obtained in the absence of pain (the baseline electrocardiogram) and for patients with pain while in hospital an electrocardiogram made during pain (the pain electrocardiogram).

Blood samples for measurement of activities of creatine kinase or its isoenzymes or both were obtained at least once before start of trial medication and every six hours until 54 hours thereafter. The activities of glutamic oxaloacetic and pyruvic transaminases, lactic acid dehydrogenase, and α hydroxybutyric acid dehydrogenase were determined every 24 hours. After 54 hours enzyme measurements were left to local routine but were recorded when available. All enzyme determinations were performed locally and were subsequently related to local normal values. Heart rate was recorded every hour and blood pressure every six hours.

Cardiac catheterisation and coronary angiography, unless contraindicated, were performed preferably before discharge but not within 54 hours after start of trial medication.

DEFINITION OF OUTCOME EVENTS AND DATA ANALYSIS

A patient was classified as having "pre-randomisation myocardial infarction" when concentrations of one or more cardiac enzymes measured before the start of trial medication were significantly raised—that is, to more than twice the local upper limit for normal. In this case no outcome classification was defined. For all other patients the following two out-

come events were defined: recurrent ischaemia or myocardial infarction within 48 hours—that is, chest pain with ST-T changes and/or enzymatic evidence of infarction as defined below; myocardial infarction within 48 hours—that is, cardiac death or characteristic serial enzyme pattern with at least one cardiac enzyme significantly raised within 54 hours (as there is an intrinsic delay in the release of enzymes after the onset of myocardial infarction enzyme values until 54 hours after randomisation were taken into account). Myocardial infarction which occurred within the remainder of the first seven days was recorded according to clinical diagnosis. For all cases classified as myocardial infarction within 48 hours the most likely time of onset was determined retrospectively from the complete clinical history. In addition, the time of appearance of a Q wave lasting $>0{\cdot}03$ seconds or of a Q wave equivalent ($R > 0{\cdot}03$ seconds in V1 and $R/S > 1$ in V2) was noted.

Those patients for whom an unequivocal protocol violation occurred before the start of trial medication were excluded from analysis. These exclusions were applied retrospectively by the Classification Committee. Patients were retained, however, if the committee disagreed with the attending physician's assessment of qualifying ST-T abnormalities or changes. Treatment effects were assessed in terms of the occurrence of the two outcome events defined above. In accordance with the protocol, patients classified as having pre-randomisation myocardial infarction were excluded from this assessment. Treatment effects were expressed as the ratio of the rate of the respective outcome event observed in patients allocated to a specific index trial medication to that observed in patients allocated to a specific reference trial medication. For instance, the effect of nifedipine relative to placebo is the rate of the outcome event in the nifedipine group divided by that in the placebo group. Thus a rate ratio of one indicates that nifedipine has no effect relative to placebo. A rate ratio of <1 points to a preventive effect and a rate ratio >1 to a detrimental effect. The 95% confidence intervals of the rate ratio estimates are also given.

We used a composite logistic prediction function to determine which baseline characteristics were independently related to the risk of recurrent ischaemia or myocardial infarction within 48 hours. The baseline risk of recurrent ischaemia or myocardial infarction within 48 hours (that is, the probability that such an event would occur) was estimated for each patient separately given individual baseline characteristics and the prediction function. Patients were subsequently divided into three subgroups of low, medium, and high risk.

In the analysis we found that despite random allocation, trial medication groups differed in terms of the distribution of baseline risk. To adjust for this, relative treatment effects, as defined above, were estimated as weighted averages of risk subgroup specific effects. Full details of the analytic methods are given in appendix II.

STUDY SIZE REQUIREMENTS

The protocol stated that trial treatments were to be evaluated in terms of the rates of recurrent ischaemia or myocardial infarction within 48 hours in patients without myocardial infarction at the start of trial medication. If it is assumed that this rate would be 40% in placebo treated patients who were not already on β blockade, that nifedipine and metoprolol alone would reduce this rate to 20%, and that the combination would reduce this further to 10% (that is event rates of 40%, 20%, 20%, and 10% respectively), 70 patients per group are required for a 97% chance of obtaining a statistically significant ($p < 0{\cdot}05$) result in a 4×2 contingency table χ^2 test.[17] To allow for lower rates and the possibility that only the combination would be effective, we planned to study 150 patients per group.

Results

RECRUITMENT AND EXCLUSIONS

Between 1 February 1981 and 30 October 1984, 668 patients were enrolled. The median contribution per centre was 50 patients, ranging from seven (for a centre that participated only during the last nine months) to 144. Randomisation by centre resulted in balanced trial medication groups.

Figure 1 shows that a violation of the admission protocol occurred in 131 patients; these cases were excluded. Another 22 patients classified as having pre-randomisation myocardial infarction were left out from trial medication assessment. In 82% of the 515 remaining patients the treating physician's judgement on qualifying ST-T abnormalities or changes was independently confirmed by the Classification Committee. Figure 1 also shows the overall occurrence of relevant clinical events. All deaths were caused by myocardial infarction.

Figure 2 shows the time of onset in 89 cases of non-fatal myocardial infarction within 48 hours of the start of trial medication. In 43 patients acute myocardial infarction was thought to have occurred before the start of trial medication despite cardiac enzyme concentrations being below twice the upper limit for normal at that time. Figure 2 also shows the time of first occurrence of a significant rise in enzyme concentrations and that of a new Q wave.

Table 1 shows selected baseline characteristics in

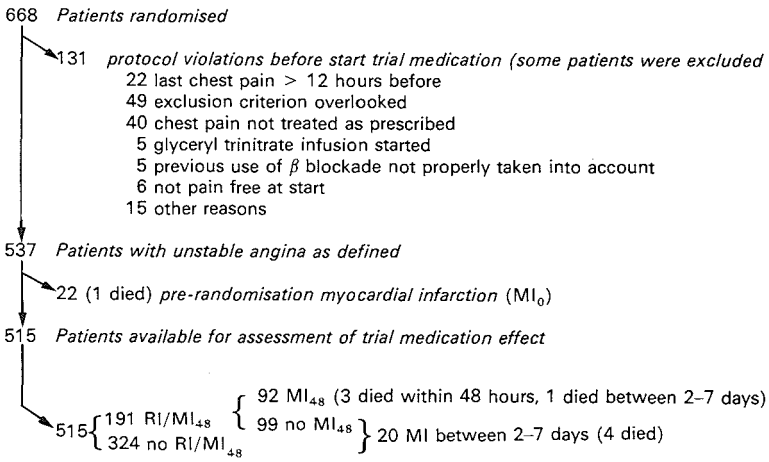

Fig 1 *Exclusions from data analysis and overall distributions of outcome events. MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours.*

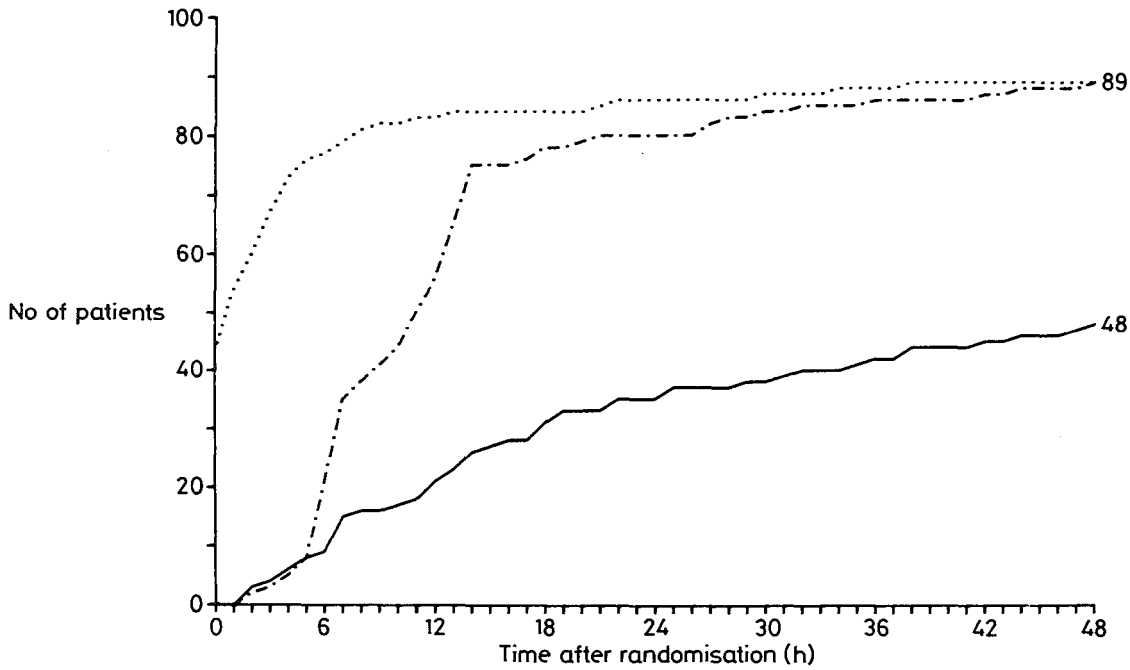

Fig 2 *Timing of the onset of non-fatal myocardial infarction, the first significant rise in enzyme concentration, and the appearance of Q waves for 89 cases of non-fatal myocardial infarction within 48 hours in 515 patients without enzymatic evidence of infarction at randomisation. The time of the onset of myocardial infarction was determined retrospectively by the Classification Committee from the complete clinical history. The upper dotted line represents the cumulative distribution of the time of onset of myocardial infarction—that is, it represents for each point in time after randomisation the total number of patients with an onset before that time. In 43 cases the onset was judged to have taken place before randomisation; the upper line thus starts at 43. Similarly the middle broken line represents the cumulative distribution of the time of first rise in enzyme concentration to over twice the local upper limit of normal and the lower solid line the time of first appearance of a Q wave on the electrocardiogram.*

Table 1 *Baseline characteristics and corresponding outcome event rates*

		RI/MI_{48}	MI_{48}
All patients	(515 = 100%)	191 (37%)	92 (18%)
Age:			
<55 years	(183 = 36%)	69 (38%)	38 (21%)
55–65 years	(248 = 48%)	92 (37%)	40 (16%)
>65 years	(84 = 16%)	30 (36%)	14 (17%)
Sex:			
Male	(387 = 75%)	149 (39%)	82 (21%)
Female	(128 = 25%)	42 (33%)	10 (8%)
History of myocardial infarction:			
No	(340 = 66%)	134 (39%)	68 (20%)
Yes	(175 = 34%)	57 (33%)	24 (14%)
History of angina >4 weeks:			
No	(308 = 60%)	116 (38%)	61 (20%)
Yes	(207 = 40%)	75 (36%)	31 (15%)
Previous maintenance treatment with a β blocker:			
No	(338 = 66%)	121 (36%)	63 (19%)
Yes	(177 = 34%)	70 (40%)	29 (16%)
Pain free interval:			
<1 hour	(133 = 26%)	82 (62%)	45 (34%)
1–3 hours	(186 = 36%)	66 (35%)	31 (17%)
>3 hours	(196 = 38%)	43 (22%)	16 (8%)
Baseline ECG:			
Not codable	(20 = 4%)	8 (40%)	6 (30%)
No ST depression ≥0·1 mV	(402 = 78%)	136 (34%)	60 (15%)
ST depression ≥0·1 mV	(93 = 18%)	47 (51%)	26 (28%)
Comparison of pain ECG with baseline ECG:			
Not possible*	(223 = 43%)	48 (22%)	24 (11%)
Same ST coding	(82 = 16%)	32 (39%)	11 (13%)
More ST depression†	(159 = 31%)	87 (55%)	45 (28%)
More ST elevation†	(101 = 20%)	60 (59%)	32 (32%)
Baseline risk for RI/MI_{48}:‡			
Low	(303 = 59%)	65 (21%)	28 (9%)
Medium	(126 = 24%)	67 (53%)	28 (22%)
High	(86 = 17%)	59 (69%)	36 (42%)

RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; ECG, electrocardiogram.
*No pain observed after hospital admission or no (codable) pain free electrocardiogram available for comparison.
†Including 50 patients who had more ST depression as well as more ST elevation.
‡As estimated from previous maintenance treatment with a β blocker, pain free interval, baseline electrocardiogram, and comparison of pain electrocardiogram with baseline electrocardiogram (see appendix II).

relation to the defined outcome events. There were only small differences between the rates of recurrent ischaemia or myocardial infarction within 48 hours of the start of trial medication for respective categories of age, sex, history of coronary disease, and previous β blockade. Trial medication was started after a pain free interval of less than one hour in 26% of patients and in a further 36% after an interval of between one and three hours. The length of this interval was strongly related to the rate of recurrent ischaemia or myocardial infarction within 48 hours: 62% of patients who had a pain free interval of less than one hour developed recurrent ischaemia or myocardial infarction within 48 hours as opposed to 22% of those in whom the pain free interval lasted more than three hours (table 1). The rate of recurrent ischaemia and myocardial infarction within 48 hours was also related to the presence of ST depressions >0·1 mV on the baseline electrocardiogram. Patients without pain observed while in hospital had a lower event rate than those with pain. In those with pain the event rate was also related to the presence of changes in ST coding during pain.

Of the baseline characteristics listed in table 1, previous use of β blockers, pain free interval before the start of trial medication, and ST coding of electrocardiograms made during and after pain were retained in the logistic function for the estimation of the baseline risk for recurrent ischaemia or myocardial infarction within 48 hours. Based on this estimation, 59% of patients were grouped as "low", 24% as "medium", and 17% as "high" risk. The observed rates were 21%, 53% and 69% respectively. The rate of myocardial infarction within 48 hours was also strongly related to this stratification. Appendix II gives full details of the logistic function.

COMPARABILITY OF TRIAL MEDICATION GROUPS AND USE OF CONCOMITANT MEDICATION

Table 2 shows the trial medication allocation. Of 338 patients who were not on previous maintenance treatment with a β blocker 84 were assigned to placebo, 89 to nifedipine, 79 to metoprolol, and 86 to the combination. Placebo was added to continued β

Table 2 *Distribution of baseline characteristics between trial medication groups*

	All	No previous maintenance treatment with a β blocker				Previous maintenance treatment with a β blocker	
		Placebo	Nifedipine	Metoprolol	Combination	Placebo	Nifedipine
Number of allocations	515	84	89	79	86	81	96
Age:							
<55 years	36%	40%	38%	41%	38%	31%	26%
55–65 years	48%	44%	49%	42%	42%	54%	56%
>65 years	16%	15%	12%	18%	20%	15%	18%
Sex:							
Male	75%	71%	74%	81%	73%	77%	75%
Female	25%	29%	26%	19%	27%	23%	25%
History of myocardial infarction:							
No	66%	73%	69%	73%	71%	49%	61%
Yes	34%	27%	31%	27%	29%	51%	39%
History of angina longer than 4 weeks:							
No	60%	69%	72%	76%	62%	46%	37%
Yes	40%	31%	28%	24%	38%	54%	63%
Previous maintenance treatment with a β blocker:							
No	66%	100%	100%	100%	100%	0%	0%
Yes	34%	0%	0%	0%	0%	100%	100%
Pain free interval:							
<1 hour	26%	23%	33%	23%	27%	27%	23%
1–3 hours	36%	27%	36%	47%	34%	35%	39%
>3 hours	38%	50%	31%	30%	40%	38%	39%
Baseline ECG:							
Not codable	4%	6%	3%	3%	5%	2%	4%
No ST depression ⩾0·1 mV	78%	76%	88%	87%	79%	63%	75%
ST depression ⩾0·1 mV	18%	18%	9%	10%	16%	35%	21%
Comparison of pain ECG with baseline ECG:							
Not possible*	43%	46%	39%	33%	48%	42%	50%
Same ST coding	16%	15%	19%	18%	14%	16%	14%
More ST depression†	31%	29%	30%	41%	26%	33%	28%
More ST elevation†	20%	17%	24%	19%	17%	22%	19%
Baseline risk of RI/MI_{48}:‡							
Low	59%	67%	60%	66%	65%	42%	54%
Medium	24%	26%	22%	29%	23%	22%	24%
High	17%	7%	18%	5%	12%	36%	22%

RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; ECG, electrocardiogram.
*No pain observed after hospital admission or no (codable) pain free electrocardiogram available for comparison.
†Including 50 patients who had greater ST depression and greater ST elevation.
‡As estimated from previous maintenance treatment with β blocker, pain free interval, baseline electrocardiogram, and comparison of pain electrocardiogram with baseline electrocardiogram (see appendix II).

blocker treatment in 81 patients and nifedipine in 96. Table 2 also shows the baseline characteristics for each trial medication group separately. Baseline risk for recurrent ischaemia or myocardial infarction within 48 hours was distributed differently over the trial medication groups. Among patients not on previous maintenance treatment with a β blocker 18% of those allocated to nifedipine were high risk; for the other three trial medication groups this percentage ranged from 5% to 12%. The higher risk of the nifedipine group was due primarily to a relatively large proportion (33%) of patients in whom trial medication was started within one hour after the last attack of pain (a strong indicator of risk, table 1). In

Table 3 *Use of trial medication at randomisation and during follow up for each trial medication group*

		Use in relation to randomisation			
		At randomisation	+6 h	+24 h	+48 h
No previous maintenance treatment with a β blocker					
Placebo	(n = 84)	100%	94%	86%	76%
Nifedipine	(n = 89)	100%	87%	71%	63%
Metoprolol	(n = 79)	100%	99%	82%	73%
Combination	(n = 86)	100%	94%	80%	70%
On continued maintenance treatment with a β blocker					
Placebo	(n = 81)	100%	89%	70%	65%
Nifedipine	(n = 96)	100%	92%	80%	74%

Table 4 *Outcome event rates in trial medication groups stratified for estimated baseline risk for recurrent ischaemia or myocardial infarction within 48 hours*

	MI_0	No MI_0	RI/MI_{48}	MI_{48}	MI_{48} + Q
No previous maintenance treatment with a β blocker					
Placebo:					
All patients	3	84	31 (37%)	13 (15%)	9 (11%)
Low risk		56	13 (23%)	3 (5%)	2 (4%)
Medium risk		22	13 (59%)	8 (36%)	6 (27%)
High risk		6	5 (83%)	2 (33%)	1 (17%)
Nifedipine:					
All patients	4	89	42 (47%)	25 (28%)	14 (16%)
Low risk		53	15 (28%)	8 (15%)	4 (8%)
Medium risk		20	14 (70%)	6 (30%)	4 (20%)
High risk		16	13 (81%)	11 (69%)	6 (38%)
Metoprolol:					
All patients	4	79	22 (28%)	13 (16%)	6 (8%)
Low risk		52	10 (19%)	6 (12%)	2 (4%)
Medium risk		23	9 (39%)	5 (22%)	3 (13%)
High risk		4	3 (75%)	2 (50%)	1 (25%)
Combination:					
All patients	7	86	26 (30%)	12 (14%)	7 (8%)
Low risk		56	9 (16%)	4 (7%)	3 (5%)
Medium risk		20	12 (60%)	5 (25%)	2 (10%)
High risk		10	5 (50%)	3 (30%)	2 (20%)
On continued maintenance treatment with a β blocker					
Placebo:					
All patients	2	81	41 (51%)	16 (20%)	6 (7%)
Low risk		34	8 (24%)	3 (9%)	2 (6%)
Medium risk		18	12 (67%)	2 (11%)	0 (0%)
High risk		29	21 (72%)	11 (38%)	4 (14%)
Nifedipine:					
All patients	2	96	29 (30%)	13 (14%)	6 (6%)
Low risk		52	10 (19%)	4 (8%)	0 (0%)
Medium risk		23	7 (30%)	2 (9%)	2 (9%)
High risk		21	12 (57%)	7 (33%)	4 (19%)

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours; MI_{48} + Q, myocardial infarction within 48 hours with subsequent Q wave formation.

patients who were on continued β blockade the same was true for patients allocated to placebo, although to a lesser extent.

Oral long acting nitrates had been given to 100 patients at admission to hospital and were continued in 76%. Thus 439 patients did not receive oral long acting nitrates at randomisation. These drugs were later given, on indication, to 11% of these patients. Anticoagulants (coumarins or heparin) were given to 67%. At the start of the trial or during follow up 14% received diuretics, 3% digitalis, and 3% platelet aggregation inhibiting drugs. Medication at hospital admission was not related to the risk of recurrent ischaemia or myocardial infarction within 48 hours.

Table 3 shows the percentage of patients still on trial medication 6, 12, and 48 hours after randomisation. At 48 hours the percentage of patients still on trial medication ranged from 63% of patients allocated to nifedipine who were not on previous maintenance β blockade to 76% of patients allocated to placebo who were not on previous β blockade. The predominant reasons for discontinuation of trial medication were recurrent chest pain and diagnostic findings of myocardial infarction. In five patients the trial medication code was broken within 48 hours of randomisation.

OUTCOME EVENT RATES IN TRIAL MEDICATION GROUPS AND RELATIVE EFFECTS OF TREATMENT

Table 4 shows the number of pre-randomisation infarctions by trial medication group. Also shown are the outcome event rates for patients without pre-randomisation infarction, both overall and according to stratum of baseline risk for recurrent ischaemia or myocardial infarction within 48 hours. The directions of the differences between the trial medication groups were consistent over the risk strata. In patients not on previous maintenance treatment with a β blocker who were treated with nifedipine both event rates were higher than the corresponding ones for those on placebo. This was also true for Q wave infarctions. On the other hand, in patients on metoprolol or on the combination, event rates tended to be lower than the rates for those on placebo. In patients who were already on a β blocker, the nifedipine group tended to have lower event rates than the placebo group.

Table 5 gives the estimated relative effects

Table 5 *Rate ratios with 95% confidence intervals for all trial medication comparisons*

	Adjusted rate ratio (95% confidence interval)	
	RI/MI_{48}	MI_{48}
	No previous maintenance treatment with a β blocker	
Nifedipine/placebo	1·15 (0·83, 1·64)	1·51 (0·87, 2·74)
Metoprolol/placebo	0·76 (0·49, 1·16)	1·07 (0·54, 2·09)
Combination/placebo	0·80 (0·53, 1·19)	0·88 (0·44, 1·74)
Metoprolol/nifedipine	0·66 (0·43, 0·98)	0·74 (0·40, 1·31)
Combination/nifedipine	0·68 (0·47, 0·97)	0·56 (0·30, 0·99)
Combination/metoprolol	1·06 (0·67, 1·70)	0·79 (0·39, 1·62)
	On continued maintenance treatment with a β blocker	
Nifedipine/placebo	0·68 (0·47, 0·97)	0·86 (0·45, 1·61)

RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours.

expressed as weighted averages of risk stratum specific rate ratios together with the 95% confidence intervals for all choices of index and reference trial medication.

Discussion

CLINICAL SPECTRUM OF UNSTABLE ANGINA DIAGNOSED AT ADMISSION TO CORONARY CARE UNIT

According to one widely accepted definition patients who have recent onset (effort) angina, worsening angina, or angina at rest are classified as having unstable angina provided there are no signs of acute myocardial infarction.[18] It is generally recognised that the differential diagnosis of such cases may be difficult and that myocardial infarction may have already occurred or may be about to occur. The present trial reports clinical events and their timing in 537 patients in whom unstable angina was diagnosed at admission to the coronary care unit.

This diagnosis was based on a combination of findings—angina at rest, evidence for causal myocardial ischaemia, and absence of signs of acute myocardial infarction such as persistent pain or characteristic electrocardiographic signs (a subcategory of unstable angina as defined above). Not unexpectedly in 4% (22 out of 537, fig 1) there had already been myocardial infarction with an increase in enzyme concentrations. These cases of myocardial infarction could have been diagnosed immediately had laboratory measurements been immediately available. Within a week of the start of the trial myocardial infarction had occurred in 25% (22 + 92 + 20 out of 537, fig 1). Thus there is a considerable risk of myocardial infarction during this period. Similar percentages have been reported before[1] but the time of the onset of infarction (retrospectively determined from the complete clinical history) relative to the time when the diagnosis of unstable angina was made was not given. Figure 2 shows that the onset of myocardial infarction was judged to have occurred before the start of trial medication in 43 cases and that there were 34 further cases within six hours of the start of the trial. Only few infarctions occurred later than six hours after the start of the trial. Thus so far as myocardial infarction occurs in patients diagnosed as having unstable angina, its onset tends to cluster around the time of diagnosis. The clinical implications of this finding are considerable and it shows that treatment which aims at the prevention of progression to myocardial infarction will have a limited effect because in most cases it will come too late.

Despite the high frequency of myocardial infarction, this trial supports the notion that the prognosis in patients with this type of unstable angina is good. Total one week mortality was only 1·7% (9/537, fig 1). Our results indicate that the short term risk of recurrent ischaemia or myocardial infarction is primarily related to the interval since the last attack of pain on the one hand and to the presence of resting ST abnormalities and pain related ST changes on the other (table 1 and appendix II). The first finding is understandable because by definition the condition of patients with a long interval between last pain attack and diagnosis has stabilised. The second finding accords with current views and previous findings on the relevance of electrocardiography in such patients.[1-3 19 20]

We did not attempt to relate the baseline risk of recurrent ischaemia or myocardial infarction within 48 hours to findings at subsequent coronary angiography. Unless there are compelling reasons for an emergency procedure, catheterisation is generally only carried out a few days after hospital admission at the earliest. Thus in most patients catheterisation results are not relevant to the initial management.

Does the clinical spectrum seen in the patients we studied in 1981–84 remain valid today? There does not seem to have been any major change in the initial clinical recognition of unstable angina and its differentiation from myocardial infarction or in the pharmacotherapeutic approach. On the other hand, emergency percutaneous transluminal coronary

angioplasty or bypass surgery are now increasingly offered, with good results.[21] It is unlikely, however, that the more general use of these procedures will have had any great effect on the clinical spectrum because such procedures are usually restricted to patients in whom chest pain persists despite maximal pharmacological treatment. In such cases angioplasty or bypass surgery may prevent the occurrence of myocardial infarction. Of the infarctions in the present trial only the later ones could have been prevented in this way, and there were only a few of these.

EFFECTS OF TRIAL MEDICATION

On the basis of an interim analysis enrolment in the present trial was discontinued (appendix I). This was because continuation of nifedipine monotherapy trial medication was considered to be unethical and, secondly, because there were only small differences between the other groups. The final data as presented here essentially accord with the interim data that led to this decision (tables 4 and 5, and appendix I).

Although the series is large, the trial medication groups are rather small. In a randomised trial with small groups the results may indicate differences in the baseline risk between the groups. Table 2 shows that this was indeed the case. We used an approach developed for non-experimental epidemiological studies[22] to impose risk stratification based on a composite logistic function of relevant baseline characteristics on our study group and we have expressed trial medication effects as weighted averages of stratum specific rate ratios. This approach ensures that the estimation of trial medication effect becomes independent of the distribution of baseline risk in the groups that are compared. The use of 95% confidence intervals for the rate ratios so obtained provides a better indication of the statistical strength of evidence than the customary significance levels (p values).[23]

Patients with a pre-randomisation myocardial infarction are no longer at risk of the defined outcome events. Therefore, we excluded these patients before we assessed the trial medication effects. To allow for effect analyses based on other principles the number of pre-randomisation infarctions is also given per treatment group (table 4).

Of all the treatments studied only the addition of nifedipine to previous maintenance treatment with a β blocker was clearly beneficial. None of the other trial regimens came out as being unequivocally effective. Furthermore, there was a worrying trend towards an increased risk for myocardial infarction in patients assigned to nifedipine alone. What is the explanation for these findings?

We postulate that when nifedipine is given to patients whose condition has become unstable despite maintenance treatment with a β blocker coronary spasm may play a larger role than it does in patients not on β blockade. This would explain the efficacy of additional treatment with a coronary spasmolytic agent such as nifedipine.

We do not believe that the apparent lack of effect of the other trial medications is caused by the selection of already stabilised patients, which would lead to too few potential outcome events. The event rate of recurrent ischaemia or myocardial infarction within 48 hours was considerable and accorded with the a priori design assumptions. Nevertheless, the confidence intervals given in table five do not exclude the possibility that relevant trial medication effects were missed. We believe that the most likely explanation lies in the particular clinical situation that this trial was designed to examine. The trial design assumed that neither ischaemia nor necrosis was present after eligibility had been established. We realised that because there are no specific early electrocardiographic signs of necrosis inclusion of some patients in whom myocardial infarction was already evolving would be unavoidable. Although we appreciated that enzyme concentrations increase within hours of the onset of myocardial infarction, we decided to exclude patients from trial medication assessment only if enzymes were already significantly raised at randomisation. This was decided for two reasons. Firstly, if enzyme measurements obtained after randomisation were used as a basis for exclusion the validity of comparisons between trial medications could be compromised. This would have occurred if any of the trial medications had affected the release of enzymes from necrotic myocardium rather than the amount of necrosis. Secondly, only enzyme measurements known at that time could be relevant to the formulation of treatment guidelines based on the results of this trial. Of patients classified as having recurrent ischaemia or myocardial infarction within 48 hours and retained in the analysis, a considerable proportion (92 out of 197, table 1) sustained a myocardial infarction, generally before the start of trial medication or so soon thereafter that oral treatment could not be fully effective (fig 2). Thus an important fraction of the events on which effect estimation was based is unlikely to be affected by a preventive effect of trial medication, notwithstanding such an effect in another context. To be effective in this context a medication must not only prevent recurrent ischaemia or infarction in patients who are still at risk when treatment becomes effective but must also limit necrosis in those in whom the process of infarction has already progressed to the extent that

an otherwise detectable infarction would become undetectable by current conventional diagnostic methods. Neither nifedipine nor metoprolol are likely to meet these requirements. Nifedipine has not been shown to reduce infarct size when given to patients with myocardial infarction.[24] Animal experiments indicate that nifedipine does not protect the myocardium when given after onset of ischaemia.[25] Nor is the effect of β blockade on infarct size definitively known.

The reason why nifedipine monotherapy increases the risk of progression to myocardial infarction cannot be determined from our data. The nifedipine results may be a chance finding. On the other hand, they virtually exclude a major preventive effect of nifedipine used in this way for this indication. We do not believe that nifedipine's postulated influence on the release of enzymes[26] explains this finding—there were more Q wave infarcts in the nifedipine monotherapy group than in the placebo group (table 4). Relative to placebo, nifedipine did not raise the heart rate substantially but it reduced blood pressure. It is possible therefore that the temporary rise in heart rate in combination with a decrease in blood pressure, which has been observed before,[27] plays a role.

Nifedipine is generally accepted to be of particular value in patients with ST elevation during pain. A hundred and one patients had these features before entry (table 1). Subgroup analysis did not show that these patients especially benefited from nifedipine alone.

COMPARISON WITH OTHER STUDIES

In another trial for which patients were selected at hospital admission treatment with four 20 mg doses of nifedipine given over 24 hours was compared with placebo.[28] Eligibility for the trial, however, required more prolonged chest pain than in the present trial and patients with electrocardiographic evidence of acute infarction were not excluded. Patients were later stratified into either acute or threatened myocardial infarction groups on the basis of the presence or absence of increased enzyme concentrations and Q waves at randomisation. The group with threatened myocardial infarction resembled the patients that we studied. The rate of progression to myocardial infarction, 75% after 24 hours, was much higher, however, probably because chest pain had been present for longer. The progression rate in the nifedipine and placebo groups was similar, as was enzymatic infarct size. The number of patients who were also treated with a β blocker was not reported, so direct comparison with our results is impossible. In another trial in patients diagnosed as having "threatened infarction" treatment with propranolol was compared with conventional treatment.[5] The effect of propranolol resembled that of metoprolol in the present trial.

Treatments in patients with unstable angina after enzyme concentrations were known to be normal have been studied in several trials with varying selection criteria. In one the addition of nifedipine to a standard regimen of propranolol and long acting nitrates reduced recurrent ischaemia during a three month follow up.[29] Nifedipine without concomitant β blockade was not studied. Another trial compared a conventional step-up regimen of long acting nitrates and propranolol with increasing dosages of nifedipine during a treatment period of 14 days.[30] Overall there were no differences in recurrent ischaemia and 14% progressed to infarction in both groups. Because this trial did not have a placebo control group it is not possible to tell whether both regimens were equally effective or equally ineffective. In the subgroup of patients who were on maintenance treatment with propranolol the addition of nifedipine controlled pain more rapidly than did the addition of nitrates or an increase of the propranolol dose. On the other hand, in the subgroup of patients who were not on maintenance propranolol the administration of propranolol or nitrates or both controlled pain more rapidly than did nifedipine. Our results accord with these findings. Moreover, they provide evidence for a positive effect of a particular β blocker in patients not already on such treatment compared with placebo and for a similar effect of nifedipine in patients already using a β blocker.

CLINICAL IMPLICATIONS

The present results confirm that with currently available diagnostic methods it is impossible to reliably differentiate unstable angina from evolving myocardial infarction at admission of a patient to a coronary care unit. Many of the patients with suspected unstable angina have already sustained a myocardial infarction or are in the process of doing so.

Initial management must take into account the possible presence of evolving myocardial infarction. The first management objective therefore becomes the reduction of the total number of infarcts eventually diagnosed among this subgroup of patients, irrespective of the precise time of onset relative to the start of treatment. To achieve this treatment must both reduce the size of evolving infarctions and prevent those which are about to develop.

Our results indicate that previous use of a β blocker is an important consideration. They suggest that in patients not already on a β blocker, a β blocker is the treatment of first choice. The fixed combination of metoprolol and nifedipine had no additional

advantages. Patients with ST elevations during pain did not seem to benefit from nifedipine. Furthermore, nifedipine cannot be recommended as monotherapy because it was associated with a higher incidence of myocardial infarction. On the other hand, patients whose condition has become unstable despite maintenance treatment with a β blocker can be expected to react favourably to the addition of nifedipine to a regimen of continued β blockade.

We acknowledge with gratitude the leadership of the late Dirk Durrer, past chairman of the Executive Committee.

Appendix I

On 27 October 1984 the Policy Advisory Board was presented with the following interim classification results of 593 randomised patients who were included irrespective of protocol violations:

	MI_0	*No* MI_0	RI/MI_{48}	MI_{48}
	No previous maintenance treatment with a β blocker			
Placebo	7	86	30 (35%)	12 (14%)
Nifedipine	7	95	41 (43%)	26 (27%)
Metoprolol	6	89	28 (31%)	17 (19%)
Combination	7	88	30 (34%)	16 (18%)
	On continued maintenance treatment with a β blocker			
Placebo	5	96	44 (46%)	18 (19%)
Nifedipine	3	104	35 (34%)	15 (14%)

MI_0, pre-randomisation myocardial infarction; RI/MI_{48}, recurrent ischaemia or myocardial infarction within 48 hours; MI_{48}, myocardial infarction within 48 hours.

For myocardial infarction within 48 hours the nifedipine:placebo rate ratio was 2·0 with a 95% confidence interval (1·1, 3·6). The Policy Advisory Board recommended discontinuation of the trial on ethical grounds because of the observed adverse effect in the group on nifedipine alone and because the effects in the other groups were smaller than expected and would have required a much larger trial for adequate statistical power.

This recommendation was accepted by the Executive Committee, which included the principal investigators of the participating centres.

Measures to discontinue inclusion were put into effect immediately.

Appendix II

The baseline risk for recurrent ischaemia or myocardial infarction within 48 hours is defined as the probability that recurrent ischaemia or myocardial infarction would occur within 48 hours given the patient's baseline characteristics and trial medication assignment to placebo. To estimate a patient's baseline risk, a logistic function was fitted to the data. This function relates the probability of recurrent ischaemia or myocardial infarction within 48 hours to a set of baseline characteristics $X_1, X_2, \ldots, X_k$ using the logistic function:

$$\{1 + \exp[-(a + b_1X_1 + b_2X_2 + \ldots + b_kX_k)]\}^{-1}.$$

CODING OF BASELINE CHARACTERISTICS

As a general principle only indicator variables were used—that is variables that assume the value 1 if the property at issue is present and 0 if otherwise.

ST depression and ST elevation (measured 0·08 seconds after the J point) was scored according to the following categories: absent; $<0·5$ mm; between 0·5 and 1·0 mm; between 1·0 and 2·0 mm; between 2·0 and 5·0 mm; >5 mm. Maximum values were recorded for the following groups of leads: (1) V2; (2) V3–V5; (3) II, III, aVF; (4) I, aVL, V6. Electrocardiographic characteristics were expressed in terms of abnormalities present on the baseline electrocardiogram and of changes in the pain electrocardiogram relative to the baseline electrocardiogram. We used separate codes to indicate that the baseline or the pain electrocardiogram was not available. The latter circumstance is of clinical relevance because this would occur if the patient had arrived at the hospital after chest pain had subsided.

VARIABLE SELECTION

We used data on all patients to fit the logistic function. Variables indicating the patient's trial medication and pre-treatment with a β blocker were kept in the model all the time.

Baseline characteristics were selected for inclusion in the model on the basis of their overall (statistical) contribution to prediction and on medical plausibility. None of the characteristics related to the patient's history or medication before admission to hospital was selected. Only the interval since the last attack of chest pain and certain electrocardiographic characteristics proved to be predictive for recurrent ischaemia or myocardial infarction within 48 hours.

Table 6 *Indicator variables (with coefficients and standard errors) retained in the logistic function of the baseline risk for recurrent ischaemia or myocardial infarction within 48 hours*

Indicator	*Coefficient*	*Standard error*	*Patients**
Pre-treatment with a β blocker	0·402	0·352	177
Pain free interval < 1 hour	1·228	0·290	133
Pain free interval between 1–3 hours	0·414	0·254	186
Baseline ECG missing	0·246	0·533	20
ST depression $\geqslant$0·1 mV on baseline ECG	0·713	0·271	93
Pain ECG absent	−0·460	0·304	203
More ST depression during pain than at baseline	0·558	0·258	159
More ST elevation during pain than at baseline	0·731	0·271	101
Constant	−1·252	0·354	515

ECG, electrocardiogram.
*Number of patients in whom the property considered was present.

The baseline risk function was obtained by setting the variables representing the patient's actual trial medication to values representing treatment with placebo.

Table 6 shows the variables that were eventually retained in the model with their coefficients and standard errors.

STRATIFIED ANALYSIS

Patients were ranked on the basis of their calculated baseline risk and were subsequently divided into three strata of low, medium, and high risk. The cut-off points were chosen so that each stratum contained an equal number of patients in whom recurrent ischaemia or myocardial infarction within 48 hours had occurred. We calculated rate ratios as weighted averages of the stratum specific rate ratios for each trial medication comparison and for each variable of interest,[31] and thus adjusted for variability of the baseline risk. Confidence limits were calculated accordingly.

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Samenvatting

Patiënten die een aanval van langdurige pijn op de borst in rust doormaken en medische hulp zoeken, worden in het algemeen naar een hartbewakingsafdeling doorverwezen wanneer de symptomen een acuut cardiaal lijden suggereren. De symptomen van deze patiënten tonen een breed spectrum, dat variëert van een beeld dat karakteristiek is voor een zich ontwikkelend hartinfarct tot klachten van pijn op de borst die niet aan myocardischaemie gerelateerd lijken. Tussen deze uitersten kan het syndroom van onstabiele angina pectoris worden onderscheiden: angineuze pijn in rust, op basis van ischaemie van de hartspier waarbij geen (substantiële) necrose van hartspierweefsel lijkt op te (gaan) treden.

In 1981 werd onder auspiciën van het Interuniversitair Cardiologisch Instituut Nederland de 'Holland Interuniversity Nifedipine/metoprolol Trial (HINT) opgezet. Doelstelling van dit gerandomiseerde, dubbel-blinde en placebo-gecontroleerde onderzoek was na te gaan in welke mate de calciumantagonist nifedipine en de beta-receptor blokkerende stof metoprolol (alleen of in combinatie) nieuwe ischaemische episodes en de ontwikkeling van een hartinfarct voorkomen bij patiënten die bij opname in het ziekenhuis vermoedelijk een episode van onstabiela angina pectoris doormaken. De klinische effectiviteit van deze stoffen bij deze indicatie was op dat moment slechts in beperkte mate onderzocht. Aan het onderzoek werd medewerking verleend door de acht cardiologische afdelingen die aangesloten zijn bij het Interuniversitair Cardiologisch Instituut Nederland en door een drietal afdelingen van grote niet-universitaire ziekenhuizen. Het onderzoek werd financiëel mogelijk gemaakt door het Ministerie van Onderwijs via het Interuniversitair Cardiologisch Instituut Nederland. Tevens werden subsidies ontvangen van Bayer GmbH, Duitsland en Hässle AB, Zweden.

De eerste patiënt werd in het onderzoek opgenomen op 1 februari 1981. Op 30 oktober 1984 werd verdere voortzetting van het onderzoek gestaakt omdat tussentijdse gegevens de indruk wekten dat het risico op een hartinfarct hoger was bij behandeling met nifedipine alleen in vergelijking met de overige behandelingen. De belangrijkste bevindingen van dit onderzoek werden in 1986 in het British Heart Journal gepubliceerd, welke publicatie als appendix aan dit proefschrift is toegevoegd. Dit proefschrift bevat een meer gedetailleerde rapportage van dit onderzoek.

Begonnen wordt met een uiteenzetting van de pathofysiologie van onstabiele angina pectoris en een overzicht van vigerende opvattingen over behandeling. Het klinisch syndroom van onstabiele angina pectoris wordt meestal veroorzaakt door een plotseling optredende verminderde toevoer van zuurstofrijk bloed naar (een gedeelte van) de hartspier. Een gedeeltelijke of tijdelijke afsluiting van een kranslagader ten gevolge van de vorming van een thrombus op de plaats van een breuk in een atherosclerotische plaque (al dan niet in combinatie met vasoconstrictie) geldt als de meest waarschijnlijke oorzaak. In eerste instantie is het klinisch beleid erop gericht nieuwe aanvallen van pijn op de borst en de ontwikkeling van een hartinfarct te voorkomen. De behandeling bestaat uit bedrust, sedatie, en toediening van nitraten, beta-receptor blokkerende stoffen, calcium-antagonisten, of heparine (al dan niet in combinatie). Op deze wijze wordt getracht het zuurstofverbruik en de zuurstofvoorziening van de hartspier in gunstige zin te beïnvloeden. Wanneer een intensieve medicamenteuze behandeling niet voorkomt dat zich nieuwe aanvallen van pijn op de borst voordoen, onstaat een indicatie voor spoedangiografie (*Hoofdstuk 1*).

De methodologische grondslagen van klinisch interventieonderzoek worden aan een beschouwing onderworpen. Een therapeutisch experiment (clinical trial) wordt gezien als een instrument om een behandelingseffect te meten. De methodologie van een therapeutisch experiment is een afgeleide van eisen van zuiverheid (accuracy) en precisie aan een meetinstrument. Een therapeutisch experiment wordt verder gezien als een experimenteel epidemiologisch onderzoek (*Hoofdstuk 2*).

Ten behoeve van dit onderzoek werd onstabiele angina pectoris gedefiniëerd als het optreden van angineuze pijn in rust die minstens 15 minuten aanhield, en die hetzij spontaan verdween of reageerde op glyceryl trinitraat (sublinguaal of een bolusinjectie) of een kleine dosis fentanyl. Indien een episode van pijn op de borst plaats vond in het ziekenhuis, was de aanwezigheid van ST-segment of T-top veranderingen in het electrocardiogram een vereiste voor toelating tot het onderzoek. Indien de pijn reeds verdwenen was voor opname in het ziekenhuis, kon de patiënt worden toegelaten bij aanwezigheid van een afwijkend electrocardiogram, tekenen van een eerder doorgemaakt hartinfarct, of angiografisch aangetoonde vernauwingen van de kranslagaderen.

Tot het onderzoek werden 668 patiënten toegelaten. Een commissie stelde vast dat bij 131 patiënten het toelatingsprotocol niet op de juiste wijze gevolgd was. Aangezien deze patiënten geen onstabiele angina pectoris hadden volgens bovengenoemde criteria, werden ze van de verdere analyse uitgesloten. De overige 537 patiënten vormen het HINT-cohort (*Hoofdstuk 3*).

Patiënten die bij opname niet reeds met een beta-receptor blokkerende stof werden voorbehandeld, werden behandeld met nifedipine-placebo en metoprolol-placebo, nifedipine (6 × 10 mg/24 u) en metoprolol-placebo, nifedipine-placebo en metoprolol (2 × 100 mg/24 u), of de combinatie van beide actieve stoffen. Bij patiënten die bij opname reeds met een beta-receptor blokkerende stof werden behandeld, werd naast voortzetting van deze behandeling nifedipine placebo of nifedipine (6 × 10 mg/24 u) als onderzoeksbehandeling ingesteld. Patiënten die bij opname reeds werden behandeld met nifedipine, werden van het onderzoek uitgesloten. Patiënten werden a-select (random) toegewezen aan één van bovengenoemde behandelingen. Deze werd vervolgens gedurende minstens 48 uur voortgezet, tenzij zich een contra-indicatie voordeed. Het effect van de behandelingen werd afgemeten aan het optreden van nieuwe ischaemische episodes (pijn op de borst met veranderingen in het electrocardiogram) of de ontwikkeling van een hartinfarct (stijging van de hartenzymen) binnen de observatieperiode van 48 uur. Een commissie bestaande uit drie ervaren cardiologen heeft voor iedere patiënt vastgesteld of en zo ja, welke van bovengenoemde gebeurtenissen zich hadden voorgedaan. De leden van de commissie waren niet op de hoogte van de feitelijke behandeling. Bij 4% van de 537 patiënten bleken de hartenzymen reeds verhoogd op het moment van randomisatie; 8% was bezig met het doormaken van een acuut hartinfarct; 9% maakte een hartinfarct door binnen 48 uur; 19% maakte binnen 48 uur een of meerdere nieuwe episodes van pijn op de borst (zonder infarcering) door; de overige 60% had een ongecompliceerd beloop over de eerste 48 uur. Onder patiënten die bij opname niet reeds werden voorbehandeld met een beta-receptor blokkerende stof, deed zich een ischaemische episode of een hartinfarct voor bij 37% van 84 met placebo behandelde patiënten; onder nifedipine bij 47% van 89 patiënten; onder metoprolol bij 28% van 79 patiënten; en onder gecombineerde behandeling bij 30% van 86 patiënten. Bij patiënten die bij opname reeds voorbehandeld waren met een beta-receptor blokkerende stof, deed zich een ischaemische episode of een hartinfarct voor bij 51% van 81 met placebo behandelde patiënten en bij 30% van 96 met nifedipine behandelde patiënten. De gebeurtenissen die optraden, betroffen in de helft van de gevallen een hartinfarct en in de andere helft een aanval van pijn op de borst met ST-segment of T-top veranderingen (*Hoofdstuk 4*).

Het effect van actieve medicatie werd (ten opzichte van placebo) uitgedrukt als de ratio van het percentage patiënten waarbij een ischaemische episode of een hartinfarct was opgetreden onder actieve medicatie ten opzichte van placebo (het relatieve risico). Een relatief risico van 1 duidt op gelijke effectiviteit van de vergeleken stoffen, een waarde kleiner dan 1 op een gunstige werking van het actieve preparaat en een waarde groter dan 1 op een ongunstige werking. De onzekerheid in de schatting van het behandelingseffect werd aangegeven met het 95%-betrouwbaarheidsinterval. Uit een multivariate analyse bleek dat het uitgangsrisico voor het optreden van een ischaemische episode of een hartinfarct hoofdzakelijk bepaald werd door de duur van de periode waarover de patiënt reeds pijnvrij was, en bepaalde electrocardiografische afwijkingen. Het uitgangsrisico voor het optreden van een ischaemische episode of een hartinfarct bleek ongelijk verdeeld over de behandelingsgroepen. Bij de schatting van behandelingseffecten werd hiervoor gecorrigeerd door middel van gestratificeerde analyse. Onder patiënten die niet met een beta-receptor blokkerende stof waren voorbehandeld, was het (gecorrigeerde) relatieve risico 1,15 (0,83–1,64) voor nifedipine, 0,76 (0,49–1,16) voor metoprolol, en 0,80 (0,53–1,19) voor de combinatiebehandeling. (Deze relatieve risico's zijn ten opzichte van placebo; tussen haakjes staan 95%-betrouwbaarheidsintervallen). Onder patiënten die reeds met een beta-receptor blokkerende stof waren voorbehandeld, was het relative risico voor (toevoeging van) nifedipine 0,68 (0,47–0,97) (*Hoofdstuk 5*).

De praktische uitvoering van het onderzoek wordt beschreven (*Hoofdstuk 6*), alsmede de gegevens en de overwegingen die een rol gespeeld hebben bij de voortijdige beëindiging van het onderzoek (*Hoofdstuk 7*).

Bevindingen van andere recent gepubliceerde gerandomiseerde onderzoekingen naar het effect van beta-receptor blokkerende stoffen of calciumantagonisten bij patiënten met klachten duidend op acute ischaemie van de hartspier worden aan een kritische beschouwing onderworpen. Speciale aandacht wordt besteed aan de generalizeerbaarheid van de bevindingen naar klinisch herkenbare indicaties (*Hoofdstuk 8*).

De bevindingen van HINT, tezamen met die van andere recent gepubliceerde onderzoekingen naar het effect van beta-receptor blokkerende stoffen bij patiënten met een vermoedelijk hartinfarct, geven aan dat behandeling met metoprolol (of met andere beta-receptor blokkerende stoffen zoals atenolol) het klinisch beloop bij klachten duidend op acute ischaemie van de hartspier in beperkte mate in gunstige zin beïnvloedt. De bevindingen van HINT, tezamen met die van andere onderzoekingen, wijzen erop dat behandeling met nifedipine het klinisch beloop bij dezelfde indicatie niet in gunstige zin beïnvloedt. Echter, wanneer het klinisch beeld van onstabiele angina pectoris ontstaan in rust zich ontwikkelt ondanks chronische behandeling met een beta-receptor blokkerende stof, lijkt toevoeging van nifedipine het klinisch beloop in gunstige zin te beïnvloeden (*Hoofdstuk 9*).

Het Engelstalige gedeelte van dit proefschrift zal in een supplement van het *European Heart Journal* worden gepubliceerd. De cardiologen S. Goldstein (Detroit), D. G. Julian (Newcastle upon Tyne), en H. Kulbertus (Luik) is gevraagd hun conclusies uit de bevindingen van het HINT-onderzoek te verwoorden. Dit commentaar zal worden opgenomen in bovengenoemd supplement.

Woorden van dank

Het in dit proefschrift beschreven onderzoek is het resultaat van de inspanning van vele anderen naast de auteur. Ik wil allen die bijgedragen hebben tot de totstandkoming van dit werk bedanken.

Een bijzondere plaats wordt hierbij ingenomen door de patiënten die bereid geweest zijn deel te nemen aan dit onderzoek. Ik hoop dat toekomstige patiënten voordeel zullen hebben van hun hereidwillige medewerking.

Daarnaast dank ik het Interuniversitair Cardiologisch Instituut Nederland voor het opzetten van de infrastructuur waarin dit onderzoek kon worden uitgevoerd en het Thoraxcentrum te Rotterdam voor het creëren van de werkomgeving van waaruit het onderzoek kon worden gecoördineerd.

Koos Lubsen heeft leiding gegeven aan de uitvoering van het onderzoek. Zonder zijn voortdurende steun en stimulans zou dit proefschrift er niet gekomen zijn. Zijn door Professor P. G. Hugenholtz gesteunde opvatting dat voor goed klinisch onderzoek een combinatie van klinische expertise en epidemiologisch/statistische deskundigheid een vereiste is, heeft geleid tot de totstandkoming van de afdeling klinische epidemiologie binnen het Thoraxcentrum. Dit proefschrift werd geconcipiëerd vanuit dezelfde invalshoek. Het is een voorrecht betrokken geweest te zijn bij zijn wetenschappelijk werk. Ik heb daar veel van geleerd en zeg hem daarvoor en voor de vriendschappelijke wijze waarop we samenwerkten, hartelijk dank.

Maarten Simoons heeft een onmisbare rol vervuld zowel bij de uitvoering van het onderzoek als bij de totstandkoming van dit proefschrift. Vanaf mijn eerste schreden in het Thoraxcentrum hebben zijn positieve invloed en vertrouwen mij zeer geïnspireerd. Naast zijn inbreng bij de verwerving van de benodigde klinisch cardiologische kennis was ook zijn scherpzinnige kritiek op methodologisch- epidemiologisch dogma van onschatbare waarde.

De overige leden van de promotie-commissie, Professor P. G. Hugenholtz, Professor Dr F. L. Meijler en Professor Dr J. P. Vandenbroucke hebben het manuscript van commentaar voorzien. Hun opbouwende kritiek heb ik in hoge mate gewaardeerd.

Verder ben ik veel verschuldigd aan al degenen die meegewerkt hebben aan de uitvoering van het onderzoek. De langdurige ondersteuning van de Wetenschappelijke Raad van het Interuniversitair Cardiologisch Instituut Nederland, voor deze gelegenheid aangevuld met de hoofden van de deelnemende niet-universitaire klinieken, voor zowel het onderzoek als de voorbereiding van het proefschrift heb ik zeer op prijs gesteld. Het onderzoek werd begonnen onder het inspirerend voorzitterschap van wijlen Professor Dr D. Durrer en werd voltooid nadat Professor Dr F. L. Meijler deze taak had overgenomen. I thank the members of the Policy Advisory Board for improving the design and execution of the trial and for assuming the responsibilities of treatment monitoring. De bijdrage van de leden van de classificatie-commissie kan alleen worden omschreven met het adjectief 'kolossaal'. Rapporten van een kleine 700 patiënten (met in totaal ongeveer 10.000 electrocardiogrammen) werden tot in de kleinste details beoordeeld. Ik heb de vriendschappelijke en professionele atmosfeer tijdens de vaak langdurige avond- en weekendsessies zeer op prijs gesteld. Ik ben hen (en hun gezinsleden) zeer erkentelijk voor deze bijdrage.

De medewerkers van het coördinatie-centrum hebben, ieder op zijn of haar eigen wijze, bijgedragen aan de uitvoering van het onderzoek, waarvoor ik hen hartelijk bedank. Jurn Kerkkamp heeft een belangrijke bijdrage geleverd aan de coördinatie van het onderzoek en heeft het electrocardiografische en angiografische gegevensbestand opgebouwd. Ron van Domburg heeft de programmatuur voor de geautomatiseerde gegevensverwerking verzorgd. Sophie van der Does, Marja Smits, en Yolande te Giffel hebben mijn soms chaotische administratieve verlangens op onnavolgbare wijze verwezenlijkt. Pieter Vrijdag heeft alle gegevens, nadat ze ingevoerd waren, nogmaals met de oorspronkelijke gegevens vergeleken. Verder zijn Marianne Bokslag en Gretta Bédier de Prairie bijgesprongen op momenten waarop dat nodig was. Nella Speelman is in al die jaren de organisatorische en secretariële spil van de afdeling geweest en heeft uit dien hoofde een belangrijke rol vervuld bij de totstandkoming van dit proefschrift.

Zonder de medewerking van de klinische centra had het onderzoek nooit kunnen worden uitgevoerd. Ik dank de betrokken medewerkers, in het bijzonder diegenen die zich ingezet hebben voor de locale coördinatie, niet alleen voor de medewerking maar ook voor de prettige manier waarop we samenwerkten.

Verder dank ik de medewerkers van het Thoraxcentrum voor de stimulerende werkomgeving, in het bijzonder Jaap Deckers en Pim de Feijter voor hun

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I thank the editors of the *European Heart Journal* for reviewing the manuscript and the staff of Academic Press London, in particular Michael Poulson, for editing the manuscript.

Dit proefschrift vormt slechts een stap in een opleiding die nooit voltooid zal zijn. Ik dank mijn ouders voor de vanzelfsprekendheid waarmee zij mij lieten studeren. Wijlen Professor H. de Jonge heeft een belangrijke rol gespeeld in mijn medisch-statistische opleiding. Professor Olli Miettinen has been a major influence in my epidemiologic education. His 1983 Hartenark course on theoretical epidemiology has been a turning-point in my development as a medical scientist.

Sylvia heeft altijd begrip getoond voor het feit dat mijn aandacht soms te vaak op het schrijven van dit proefschrift gericht was. Ik ben haar dankbaar voor haar nimmer aflatende ondersteuning en vooral voor haar geduld.

Curriculum vitae

Jan G. P. Tijssen werd op 10 april 1948 te Bemmel geboren. In 1966 behaalde hij het eindexamen gymnasium-B aan het Jacob Roelandscollege te Boxtel. De studie in de wiskunde (met als hoofdrichting wiskundige statistiek) aan de Katholieke Universiteit Nijmegen werd in 1972 afgesloten met het behalen van het doctoraal examen. Het daarop volgende jaar werd als 'teaching assistent' doorgebracht aan 'Wayne State University' te Detroit (USA). Van 1973 tot 1975 was hij verbonden aan de Vakgroep Wiskunde en Statistiek van de Landbouwhogeschool te Wageningen. Van 1975 tot 1980 was him werkzaam bij de afdeling Medische Statistiek van de Rijksuniversiteit Leiden, waar hij ondermeer betrokken was bij het 'Zestig-Plus-onderzoek'. Hiervoor werd hij, tezamen met de andere onderzoekers van de 'Zestig-Plus' groep, onderscheiden met de Dr Saal van Zwanenberg-prijs 1983. Vanaf 1980 is hij als wetenschappelijk medewerker verbonden aan de afdeling Klinische Epidemiologie van het Thoraxcentrum te Rotterdam, daartoe aangesteld door het Interuniversitair Cardiologisch Instituut Nederland.