PREDICTION OF CARDIAC DEATH

AN EPIDEMIOLOGICAL STUDY ON THE PROGNOSTIC SIGNIFICANCE OF 24-HOUR ECG-RECORDING

Cover design: Heleen Velema

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AN EPIDEMIOLOGICAL STUDY ON THE PROGNOSTIC SIGNIFICANCE OF 24-HOUR ECG-RECORDING

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. J. SPERNA WEILAND
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
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TE 3.45 UUR

DOOR

JOHAN PIETER VELEMA

GEBOREN TE 'S-GRAVENHAGE

PROMOTOREN	Prof. Dr. J. Pool
	Prof. R. van Strik
CO-REFERENTEN	Prof. Dr. E.O. Robles de Medina
	Prof. Dr. J. Strackee

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dedicated to Jesus Christ
the one
who teaches me
by example
the essence of living

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PREFACE

'There is nothing so harmful as too much formal education.'
(Charley Brown)

Learning begins as soon as we are born. My parents were my first teachers. They taught me to do a job well once I had begun. They also taught me that God had created me and was ordering my life. Although it took some time, I came to see that it is indeed God who gave me my talents as well as providing opportunities to develop them. This understanding led me to dedicate this thesis to the person in whom God made himself fully known.

Although it appears that I have not heeded Charley Brown's wise words, I can justify myself by saying that this last phase of formal education wasn't really very formal at all.
I was rather being thrown in at the deep end and was expected to apply myself, including all that I had learned, to the research described in this thesis. Since I was new to both cardiology and epidemiology I needed an introduction. This was provided by Dr. J. Lubsen, who in various ways let me share in his wide experience. He entrusted this project to me and has never withdrawn his trust in me since. For this I'm very thankful as I am aware I made this difficult for him from time to time.
Prof. Dr. J. Pool provided the touch with clinical practice, which was indispensable for the present study. He knew Cardiolab (in fact he was one of its originators), knew clinical practice and at the same time he was aware of my methodological problems. In spite of his many obligations, there was always time to discuss the latest results or organisational hang-ups. I have greatly appreciated this. Many ideas and practical solutions originated in the discussions between Pool, Lubsen and myself. I'm sure the present result is as much a cause of satisfaction to them as it is to me.

Prof. R. van Strik gave me generous hospitality in the Institute of Biostatistics. I thank him for his kindness and for the interest with which he read the numerous versions of the manuscript. His sound knowledge of fundamental statistical concepts and his wide experience in their application have been a great help to me.

I also thank prof. Dr. J. Strackee who was not content to wait for the manuscript to arrive but insisted that we discuss things at a much earlier stage. His comments were valuable and reassuring.

I thank Prof. Dr. E.O. Robles de Medina for his sympathetic interest in my work and his helpful comments.

Pieter Vrijdag and Henk Kuiper, both medical students, did their third-year research project with me and assisted me with the data-collection. They were ingenious in tracing people who without them would have been inevitably lost to follow-up. I thank them for their hard work and cheerful company.
S.J.Zwarts en A.J. van Veelen did a good deal of data collection in a similar context even before I came into the scene. Their previous work gave me a good start.

In connection with the data collection, I would like to thank the many anonymous registration officers, who reacted so cooperatively to my request for information and spent considerable time answering our questions and correcting with minute precision the mistakes which we inevitably made due to shortcomings in our data.

Nella Speelman spent much time and energy in the past months typing and forever correcting the numerous versions of the manuscript which others only had to read. Her unfailing determination is one of the rocks on which the production of this thesis has been built.

I thank the Department of Epidemiology and particularly Bram van Laar for welcoming me to their computing-facility and giving the necessary assistance.

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The Thoraxcenter (head: Prof. dr. P.G. Hugenholtz) provided the facilities which enabled me to carry out the present study and thus to gain much valuable experience.

I gratefully acknowledge the help of Cardiolab (medical director Dr. J. Roelandt) which supported the project in various ways - not in the least by providing the data on which this study is based.

I also thank Angela Peterse and Suze Schenderling whose patience I taxed with endless questions.

I thank Mary Rose Hoare for her corrections with regard to the English language.

Hans Büsselmann showed admirable skill in preparing the many figures in this thesis (except for figures 1.1/1, 3.2/1 and 5.8/1). I remember the evenings we spent for this purpose as particularly enjoyable. Many thanks to him, too.

I finally thank my wife Heleen for the privilege of sharing her friendship with me under all circumstances.

Johan P. Velema

1 INTRODUCTION

Since the introduction of the string galvanometer by Einthoven (1901), various instruments have been developed (a technical review is given by Dunn & Rahm, 1950) to record the so-called electrocardiogram (ECG). Physical activity, changes in position and certain bodily functions such as digestion and sleep were found to be associated with changes in the ECG.

The ECG is therefore recorded while the patient is lying down and relaxed. The length of such a resting ECG (also referred to as standard or 12-lead ECG) varies from 10 to 45 seconds. Transient phenomena can easily be missed in this way. If desired, the length of the ECG can be extended. However, the patient is not free to move and the analysis of the large number of ECG complexes soon becomes burdensome.

1.1 Continuous recording of the electrocardiogram

In 1944, Likoff et al described an instrument for the continuous recording of the electrocardiogram. This utilized an optical system which recorded the ECG complexes on 16mm film. The minute images could be projected on a screen or photographic paper at the size of an ordinary electrocardiogram. With this instrument they made ECG-recordings of up to 10 hours of patients undergoing surgery, of patients with transient arrhythmias, patients in whom a patent ductus was being ligated and of patients approaching death. In all cases, the patient was confined to a hospital bed. It was not necessary to watch the ECG continuously while it was being recorded.

From this report, the value of continuous monitoring of the ECG was clear. It permitted study of transient phenomena and of the influence of various circumstances on the activity of the heart. Since then, electronic instruments have superseded this optical design. However, the concept of continuous ECG-recording had taken root and different lines of development can be traced in this area.

1.1.1 the cardiac monitor

When a patient is confined to a hospital bed, long continuous measurements can be made by means of a cardiac monitor according to a concept described by Haber (1959). The continuous ECG-signal is evaluated automatically and is recorded if a significant change in heart rate or in width of the QRS-complex occurs. An alarm may be sounded at the same time. This method was used by Spann et al (1964) for patients in the acute phase of myocardial infarction (MI) and by Criscitiello et al (1965) for the detection of transient arrhythmias in patients with palpitations, dizziness or syncope. It is still used today in the modern coronary care unit.

1.1.2 exercise electrocardiography

Already in the early stages of electrocardiography, there was interest in the effect of exercise on the ECG. Einthoven (1908) had his old laboratory porter climb a flight of stairs in order to study the modification provoked by physical exertion. Bengtsson (1956) mentions reports by Strubel in 1912, Rumpf in 1913 and Kahn in 1914. Goldhammer and Scherf proposed in 1932 that 'the electrocardiogram be obtained after exercise in order to diagnose coronary stenosis early and objectively' (see Scherf, 1960).

Much discussion has been devoted to the question which criteria should be used to establish this diagnosis (Scherf, 1960; Mattingly, 1960). The kind of exercise the subject should perform is also of importance. This might be a step-test as proposed by Master et al (1942), riding a bicycle ergometer (Bengtsson, 1956) or walking a treadmill (Simonson & Keys, 1956). Yu and Soffer (1952) emphasized the importance of recording the ECG during rather than just after exercise. The diagnostic value of exercise electrocardiography may be increased by computer-assisted quantitative analysis of the ECG (Simoons et al, 1981).

1.1.3 radio-electrocardiography

Solutions were sought which would permit ECG-recording without gravely interfering with the freedom of the subject. Holter (1949) was the first to use radio transmission to eliminate the cables, an idea also originating from Einthoven (1906). This only required that the subject stay within the range of the radio receiver. This method was developed further and used during standardized exercise (Bellet, 1961). In The Netherlands, Rookmaker (1969) used radio-electrocardiography to develop criteria for the diagnosis of myocardial ischaemia. Patients were asked to climb stairs, to walk in the garden and to ascend a slope while ECG-changes were noted by a cardiologist. To obviate the need for a skilled person to watch the ECG-signal continuously, Holter (1957) recorded the ECG-signal on magnetic tape and designed an instrument which allowed the analysis of this signal at 60 times the recording speed.

1.1.4 ambulatory ECG-recording

Subsequently, Holter (1961) developed an instrument, consisting of an ECG-amplifier connected to a tape recorder, which was small enough to be carried on a shoulder strap or in a handbag. With this instrument the ECG could be recorded directly instead of via radio transmission. The subject thus became free to move around and engage in any kind of activity. The necessary electrodes and cables did not greatly interfere with activity. The recorder weighed 1 kg, measured 195x98x46 mm^3 and recorded the ECG continuously for periods up to 10 hours. Smaller and lighter recorders have since been developed impeding the patient's freedom of movement even less and allowing recording periods of up to 24 hours. For the analysis of these ECG-recordings, Holter used the same instrument he had used with radio transmission. The ECG-pattern that is obtained by means of this system and the pattern obtained from a standard ECG are slightly different (Gilson et al, 1964). Critical testing of the first commercial systems led Hinkle et al (1967) to the conclusion that 'its chief value appears to lie in its contribution to the study of rate, rhythm and conduction' but that 'it is dangerous to draw any inferences about the presence or absence of heart disease because of deflections of the ST segment and T wave as recorded by the system'.

1.2 Applications of ambulatory ECG-recording

Ambulatory ECG-recording has been widely applied 1) to assess the prevalence of arrhythmias in clinically healthy subjects, 2) to study the influence of environmental factors on the occurrence of arrhythmias, 3) to document the effect of anti-arrhythmic agents and 4) to monitor patients with specific cardiac disorders.

1.2.1 clinically normal individuals

Hinkle et al (1969) were the first to use this new ECG-recording technique on a large scale. Six hour recordings were obtained from 301 actively employed men who were put through a standardized routine of activities. This provided data concerning the prevalence of different arrhythmias in a population sample. However, 20% of these subjects were known to suffer from coronary heart disease.
Studies of subjects without clinical evidence of cardiovascular disease such as the one reported by Verbaan et al (1977) have been reviewed by Winkle (1980b) and Moss (1980) with regard to ventricular arrhythmias. Prevalence of 'any premature ventricular complexes' ranged from 15% to 100% and prevalence of ventricular tachycardia from 0% to 6%. Barrett et al (1981) reviewed similar studies but also considered non-ventricular arrhythmias.

1.2.2 environmental factors

Ambulatory ECG-recording allows registration of the ECG while the subject is engaged in activities which cause psychological stress, such as driving an automobile (Bellet et al, 1968; Taggart, 1969), public speaking (Taggart et al, 1973), performing psychological tests (Hinkle, 1964), coaching football games (Gazes, 1969), or while the subject is under circumstances which cause physiological stress, such as high altitude (Sanders et al, 1966), during fasting (Wang et al, 1979), in a sauna bath (Taggart, 1972), during sports (Odink et al, 1980) or during sexual intercourse (Corday, 1965). ECGs have also been recorded during sleep (Shahaway, 1970; Lown, 1973) and in patients who had practiced relaxation therapy (Benson et al, 1975). Naturally, some of these circumstances including sleep occur during the ordinary recording of 24-hour ECGs in out-patients and contribute to the eventual results.

1.2.3 evaluation of anti-arrhythmic therapy

Reduction of the frequency with which arrhythmias occur as detected by 24-hour ECG-recording would appear to provide an objective measure of the effect of an anti-arrhythmic agent. This reduction should be measured by comparing recordings of each individual patient before and after administration of the drug. However, critical application of this method has revealed that reductions may occur as a consequence of normal variation of arrhythmic activity rather than as a result of the drug-effect (Winkle, 1978; Morganroth et al, 1978). Harrison et al (1978) state that 'in order to be absolutely certain scientifically that the drug is continuing to be efficacious, the patient would need to have periodic drug withdrawals, with control monitorings in the absence of all drugs interspersed throughout the period of follow-up'. To this must be added that the effect of any placebo treatment should also be considered.

1.2.4 patients with cardiac disorders

Hinkle et al (1969) attempted to relate the occurrence of arrhythmias to presence of coronary heart disease and subsequent cardiac death. Interest in these relationships was stimulated by observations in the coronary care unit (CCU) (Lown et al, 1967a) which indicated that sudden death, caused by ventricular fibrillation, is in turn preceded by ventricular tachycardia and other ventricular arrhythmias and that suppression of ventricular arrhythmias by means of anti-arrhythmic drug therapy prevents the occurrence of sudden death. Having proved its effectiveness in the CCU, Lown & Wolf (1971) applied the same approach to ambulatory patients. They hypothesized that sudden deaths outside the hospital were also preceded by the occurrence of ventricular arrhythmias. They suggested that detection of ventricular arrhythmias (which they later called 'transient risk factors' - Lown et al, 1975) by means of ambulatory ECG-recording could identify patients at high risk for sudden death. Such identification was necessary since the toxicity of anti-arrhythmic agents did not permit indiscriminate prescription to all patients possibly at risk for sudden death.
Lown & Wolf suggested that attention should be directed towards patients who sustained a myocardial infarction (post-MI patients) as these are at considerably greater risk for sudden death than are patients without this condition. This suggestion was followed by a large number of studies in which ambulatory ECG-recordings of varying duration were obtained from post-MI patients and the occurrence of ventricular arrhythmias related to mortality during the subsequent time interval. These studies will be reviewed in chapter 7 (see table 7.2/2).

Apart from studies of patients with coronary heart disease, Harrison et al (1976) list studies of the prevalence of arrhythmias in patients with mitral valve prolaps, Wolff-Parkinson-White syndrome, bradycardia-tachycardia syndrome, idiopathic hypertrophic subaortic stenosis, pacemaker malfunction and of patients with palpitations, dizziness or syncope. They add that 'in none of these conditions is the prognostic significance of the arrhythmias known'.

1.3 Ambulatory ECG-recording in The Netherlands

In The Netherlands, the application of 24-hour ECG-recording was facilitated by the development of a service laboratory called Cardiolab, which distributes all equipment needed for the recording of 24-hour ECGs to individual hospitals. The analysis of these ECGs, however, is done in one location (Rotterdam). This has several advantages:

- The instruments for the analysis, which are far more expensive than the recording equipment, are used efficiently.
- Standards regarding nomenclature and criteria for the detection of arrhythmias are uniform and are more easily kept up-to-date.
- Technical know-how can be concentrated among a few highly skilled, specialized people.
- Technicians who analyse these ECGs are more easily provided with continuous high-level training and do not need to combine this work with other duties.
- Quality control is easy and effective.

Cardiologists and internists from all over The Netherlands make use of the Cardiolab service. Figure 1.1/1 illustrates the growth that has taken place since its beginning in 1976. In 1981, more than 10,000 24-hour ECGs were analysed. This growth reflects the growing popularity of this non-invasive diagnostic method that is now within the reach of every hospital, however small. All that is needed in the hospital itself is a nurse or technician who has been instructed in the use of the recording equipment and in the correct application of the electrodes to the patient's chest.

Each physician is free to use his own criteria when deciding whether or not the use of ambulatory ECG-recording is indicated. However, it is possible to list several typical categories of patients for which the method is currently being used:

- Patients with symptoms. These patients present with such symptoms as palpitations, dizziness or syncope and may or may not have a history of myocardial infarction or other signs of coronary heart disease. They have usually been referred by their general practitioner to the out-patient clinic of a nearby hospital. Ambulatory 24-hour ECG-recording may reveal a temporal relationship between arrhythmias and symptoms. Alternatively, the absence of arrhythmias during symptoms may point to a non-cardiac cause for these symptoms.
- Patients who are known to have arrhythmias. Ambulatory 24-hour ECG-recording provides information about the frequency and severity of these arrhythmias. It may also reveal, for instance, that a patient with frequent premature ventricular complexes occasionally has short runs of ventricular tachycardia as well. Information of this kind will be an aid in deciding on the appropriate therapy.
- Patients who are on anti-arrhythmic therapy. The effect of anti-arrhythmic therapy may be evaluated by comparing 24-hour ECGs

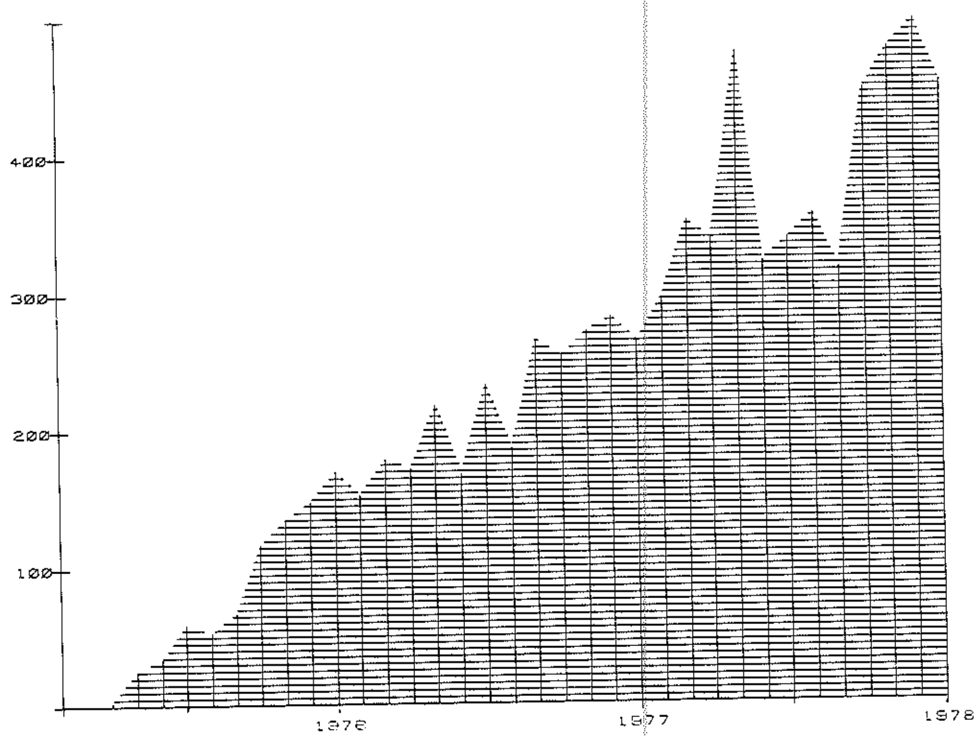


Figure 1.1/1
Number of tapes analysed by Carbiolab per month. Each horizontal line represents 5 tapes, each vertical line represents 1 month.

recorded before and after their administration. Often, however, patients are monitored who have been on anti-arrhythmic therapy for some time but continue to have symptoms. If the arrhythmias are found to persist, a change of therapy is indicated.

- Patients in whom a pacemaker has been implanted. Such patients sometimes present with symptoms which may point to (possibly intermittent) malfunction of the pacemaker. When the usual methods of checking the pacemaker fail to detect any errors, a 24-hour ECG may be helpful.

1.4 Objective of the present study

The present study was designed to investigate whether prognostic information can be derived from a 24-hour ECG which is recorded in the context of usual medical care.

It was concerned with a sample of patients for whom a 24-hour ECG was analyzed by the Cardiolab service. They came to the out-patient clinic and presented with signs and/or symptoms of such a nature, that the physician decided to have a 24-hour ECG recorded. The result of the ECG-analysis served as an aid in diagnosis and/or the selection of a treatment strategy for the individual patient. The recordings were not made to determine the prognosis of the patients.

Through the construction of prognostic equations, it was attempted to identify ECG-findings which would indicate risk of (cardiac) death given that routinely available clinical information had been taken into account. The resulting prognostic equations permit estimation of the risk of (cardiac) death.

As has been mentioned in section 1.2, earlier studies of the prognostic significance of arrhythmias have been limited to patients with specific disorders, particularly post-MI patients. The present study, rather than considering patients with one specific disorder in isolation, addresses the more pragmatical question of the prognosis of the patient with whom the cardiologist or internist is confronted in the out-patient clinic at a stage that little may be known about the underlying causes of the patient's symptoms.

2 METHODS

2.1 General outline

In order to investigate whether ECG-findings derived from ambulatory 24-hour ECG-recordings could indicate future mortality, data were collected from the archives of Cardiolab (see 1.3). Details of this organisation and its procedures are given in section 2.2.
With only a few restrictions (see 2.3), all patients of whom a 24-hour ECG had been recorded between January 1976 and June 1978 inclusive were included in the sample (N=5130).
All patients in the sample were followed through time from the date of ECG-recording either until death or until at least 18 months had passed (see 2.5). The mortality in the sample was compared with the mortality in the Dutch population (section 3.2). Cases were defined as patients who died within 18 months of 24-hour ECG-recording. Controls were randomly selected from all patients known to be alive 18 months after the 24-hour ECG was recorded (see 2.6).
It was attempted to establish relationships between baseline information (i.e. all that was known about the patient at the time of ECG-recording) and 18 month mortality. Rather than comparing all survivors with all non-survivors (the usual approach in a follow-up study), cases, who did not survive 18 months, were compared with controls, who were randomly selected from all those who did survive 18 months.
The scale of the problem was greatly reduced through this approach, while the consequent loss of statistical power was not great (see 2.4).
Baseline information, such as ECG-findings, use of medication and history of the patients' clinical condition, was collected for cases and controls from the archives of Cardiolab and from the physicians who referred these patients for 24-hour ECG-recording (see 2.7).
The prevalence of these characteristics in the entire sample was estimated from the prevalence among cases and controls, taking account of the stratified sampling scheme (see 3.1.1).
Associations of individual characteristics with mortality were studied by comparing the proportions of cases and controls in whom the characteristic was present and by considering the crude odds ratio (see 3.3).

For cases, cause of death was classified as cardiac, non-cardiac or cardiovascular (see 2.7). Cases with a cardiac cause of death were then separately compared with controls. Multivariate analysis was used to examine patient characteristics and their association with mortality in conjunction with each other (see 3.4).
Multiple logistic regression equations were constructed for the prediction of (cardiac) mortality (see 3.4.1). These equations were used to estimate the probability of (cardiac) death for the individual patient (see 3.5.1). Receiver Operating Characteristic (ROC) curves were used to represent the performance of in the resulting equations in prediction and to compare the performance value of different equations (see 3.5.2).

2.2 Instruments and procedures used by Cardiolab

2.2.1 recording

HP 14245B adhesive electrodes are used. The skin is carefully cleaned of hair and fat and the patient is instructed not to take a shower during the recording. Patients are requested to keep a diary of their daily activities and whenever symptoms occur, to note in the diary time, nature of symptoms and activities during which they were experienced. The recorder is started and a test-strip is recorded to check whether the system functions adequately. After this the patient goes home and is free to engage in any activities he or she wishes. This procedure applies to all out-patient clinics that make use of the Cardiolab service.
Portable battery-powered taperecorders (Oxford instruments, Medilog series) are used. They are light (400 grams), small (112x86x36 mm^3) and utilize ordinary Philips cassette tapes. Four channels are available of which only three are normally used: one for a signal from a clock module (30 or 60 Hz) and two for the signals of two independent ECG leads. These are a vertical lead with electrodes high (-) and low (+) on the sternum, for an optimal recognition of P-waves and a lead called CM5 with electrodes above the apex of the heart (+) and on the sternum (-). Tape speed is either 1 or 2 mm/sec. The frequency response depends on the recording and playback speeds and on the recording method (amplitude or frequency modulated). During the study period, only Medilog 1 amplitude modulated recorders were used with a frequency response in the range of 0.15 to 100 Hz.

Table 2.2/1

Categories of indication and medication which appear on the Cardiolab request form and the abbreviations used for the indications.

Indications		Medication
myocardial infarction	(MI)	digitalis
coronary heart disease	(CHD)	diuretics
palpitations	(PALP)	nitroglycerin
dizziness	(DIZZ)	anti-arrhythmics
syncope	(SYNC)	beta-blockers
evaluation of therapy	(THER)	anti-coagulants
evaluation of pacemaker	(PACE)	other
evaluation of arrhythmia	(ARRH)	
other	(OTHER)	

2.2.2 tape handling

Tapes are sent by mail to Cardiolab together with the diary, the test-strip, and a request form (see appendix). The request form contains the name, initials, address, date of birth and sex of the patient as well as the date of recording, the time the recording was started, any medication the patient is using and the indications. During the first part of the study period, the physician entered a description of any signs and symptoms together with the questions the physician hoped to have answered by this investigation. The form was later modified so that the physician could tick one or more categories of medication and indication (table 2.2/1). For the purpose of this study, written text has been categorized in the same way. The name of the patient's general practitioner is often stated on the request form as well.

2.2.3 processing

Tapes can be played back at 60 or 120 times the recording speed. The signal from the clock module is used to correct during playback for variations in the recording speed and also for the analyst to keep track of the time elapsed since the beginning of the recording.
The analyst watches the ECG complexes from both channels simultaneously on an oscilloscope. Each complex from a channel is superimposed on the one preceding it. This facilitates the detection of irregularities. An

audible signal is also produced so that irregularities can be heard as well as seen. When irregularities occur, the analyst stops the tape and a frozen picture is displayed of the ECG of the last 40 seconds from both leads. He or she then classifies the arrhythmias detected, if any. Definitions of arrhythmias as used during the study period are listed in table 2.2/2. Arrhythmias are documented on hard copy ECG-strips. During the analysis of the tape, special attention is given to the ECG recorded at times when symptoms occurred, as indicated in the diary.

2.2.4 reporting

The outcome of the analysis of the tape is reported on a report form (see appendix). The analyst scores how often a particular arrhythmia occurs on a 5-point scale with categories 0 (never), 1 (sporadic), 2 (fairly often), 3 (often), 4 (continuous). These categories have been defined in percentages of recording time as: 1 (0-10%), 2 (10-50%), 3 (50-90%), 4 (90-100%). This report form and the ECG-strips produced are seen and commented on by a cardiologist. The resulting file is sent to the physician who requested the analysis. An identical file, as well as the tape, are kept in the archive of Cardiolab. Each is uniquely identified by a number indicating the out-patient clinic where the tape was recorded and a sequential number for each tape being recorded at a particular clinic.

2.3 The sample

For the purpose of this study, all report forms which concerned recordings made between January 1976 and June 1978 inclusive were retrieved from the archives of Cardiolab. As data collection took place in the spring of 1980, sufficient time had passed between recording and follow-up. Only first reports were considered, leading to the exclusion of about 400 reports which concerned a second, third or even sixth or seventh recording of one and the same patient. It was estimated that about 50 reports of recordings made in this period could not be retrieved. Thirty-five patients under 10 years of age at the date of the 24-hour ECG were excluded as these were mostly treated for congenital diseases, which were beyond the scope of this study. The result was a sample of 5130 patients, who underwent 24-hour ECG-recording for the first time between January 1, 1976 and July 1, 1978.

Table 2.2/2
Nomenclature and criteria for the classification of arrhythmias as used in the present study

Ventricular arrhythmias	
Premature Ventricular Complex (PVC)	no associated P-wave preceding widened QRS; QRS configuration different from that of basic QRS; coupling interval shorter than basic interval.
Uniform PVCs	PVCs with identical QRS configuration
Multiform PVCs	PVCs with different QRS configuration
Bigeminy	a normal complex followed by a PVC; at least 3 of these combinations in a sequence.
Doublets	two consecutive PVCs.
Ventricular tachycardia (VT)	>2 consecutive PVCs at a rate >100/min.
Short VT	VT of 3-10 complexes.
Long VT	VT of >10 complexes.
Idioventricular rhythm	3 or more consecutive ventricular complexes (see PVC but without shorter coupling interval) at a rate <40/min.
Accelerated idioventricular rhythm	idioventricular rhythm at a rate 40-100/min.
Short ventricular arrest	pauses in ventricular activity of 2-3 sec.
Long ventricular arrest	pauses in ventricular activity of >3 sec.
Ventricular escape	widened QRS terminating a pause; no associated P-wave preceding QRS.
Ventricular flutter	regular sequence of widened QRS; rate >250/min.; QRS and T-waves cannot be clearly identified.
Ventricular fibrillation	irregular deflections, continuously changing in size, shape and direction; P, QRS and T-waves cannot be clearly identified.
Supraventricular arrhythmias	
Premature Supraventricular Complex (PSVC)	normal QRS preceded by abnormal P-wave or without associated P-wave or widened QRS preceded by abnormal P-wave; coupling interval shorter than basic interval.

Table 2.2/2 (continued)

Supraventricular tachycardia (SVT)	3 or more consecutive PSVCs at a rate >100/min.
Nodal rhythm	normal QRS preceded (PR <.12 sec.) or followed by abnormal P-wave or without associated or identifiable P-wave; rate 40-60/min.
Accelerated nodal rhythm	nodal rhythm at a rate 60-100/min.
Sinus bradycardia	heart rate <50/min.; each QRS preceded by normal P-wave.
Sinus tachycardia	heart rate >150/min.; each QRS preceded by normal P-wave.
Nodal escape	normal QRS terminating a pause; P-QRS relationship as specified for nodal rhythm.
Atrial fibrillation	no P-waves; RR totally irregular; fibrillatory waves; QRS usually normal but may be widened; ventricular response may be slow, normal or fast.
Atrial flutter	flutter waves; rate 250-350/min.; QRS usually normal but may be widened.
Sinus Arrest	pauses with PP at least 1.5 times previous PP interval but not a multiple of it.
<u>Conduction disturbances</u>	
1° AV-block	every P-wave followed by QRS; PR >.20 sec.
2° AV-block type I (Wenckebach)	not every P-wave followed by QRS; progressive lengthening of PR interval preceding blocked P-wave.
2° AV-block type II (Mobitz)	not every P-wave followed by QRS; PR interval of conducted P-waves constant.
3° AV-block	no relationship P-waves and QRS; slow ventricular rate.
Intraventricular conduction defect (IVCD)	QRS preceded by normal P-wave; QRS widened;

note: a normal P-wave is characterised by a width of .08 sec.; upright or positive-negative polarity and a PR interval >.12 sec. a widened QRS is defined as >.12 sec.

2.4 Study design

All patients in the sample were followed from the date of ECG-recording either until death or until at least 18 months had passed. Furthermore, extensive baseline information (i.e. all that is known about a patient at the date of the 24-hour ECG, see 2.2.2, 2.2.4) was available for all these patients in the archive of Cardiolab. One can thus construct for any feature F from the baseline information the 2x2 table:

	F^+	F^-	
deaths	a	b	m_1
survivors	c	d	m_0
	n_1	n_0	N

where a and b are the numbers of deaths within 18 months of the 24-hour ECG with and without F respectively, c and d are the numbers of patients with and without F who survived 18 months, $m_1=a+b$, $m_0=c+d$, $n_1=a+c$, $n_0=b+d$ and $N=m_1+m_0=n_1+n_0$ which equals the size of the sample.
The sample is assumed to be randomly drawn from an infinite population of patients of whom an ambulatory 24-hour ECG has been recorded. Similarly, the m_1 deaths and m_0 survivors are assumed to be random samples from the deaths and survivors in this population.

In order to see whether in the population presence of F involves an increased risk of death within 18 months we compare P_1, the probability of death within 18 months given the presence of F, with P_0, the probability of death within 18 months given the absence of F.
Rather than using the ratio:

$$r = P_1/P_0$$

which is called the relative risk, the measure commonly used for this purpose is:

$$\frac{P_1/(1-P_1)}{P_0/(1-P_0)} \qquad (1)$$

that is, the ratio of the odds of death given the presence of F to the odds of death given the absence of F. The odds ratio was first proposed by Cornfield in 1951 and has a number of desirable properties.
If P_1 and P_0 are small, $(1-P_1)$ and $(1-P_0)$ will be nearly equal to unity. The odds ratio is therefore a good approximation of the relative risk under this circumstance.

From the sample, the odds ratio is estimated as:

$$\frac{a/n_1 \,\big/\, c/n_1}{b/n_0 \,\big/\, d/n_0} = \frac{ad}{bc} \qquad (2)$$

The above applies to follow-up studies. Now if a patient in whom F is present is more likely to die, it follows intuitively that a patient who is known to have died is more likely to display F (Cornfield, 1951). This leads to the alternative approach of comparing the probability Q_1 that F is present in patients who are known to have died with the probability Q_0 that F is present in patients who are known to have survived (case-control studies).
Using Bayes' theorem, it can be shown that the odds ratio:

$$\frac{Q_1/(1-Q_1)}{Q_0/(1-Q_0)} \qquad (3)$$

is mathematically identical to the odds ratio (1). This is also clear when we estimate (3) from the sample as:

$$\frac{a/m_1 \,\big/\, b/m_1}{c/m_0 \,\big/\, d/m_0} = \frac{ad}{bc} \qquad (4)$$

which is identical to (2).
Because it is possible to state the problem in terms of Q_1 and Q_0, we can consider the 2x2 table given above as resulting from a case-control study with m_1 cases and m_0 controls. However, as N is of the order of 5000 and 18-month mortality is small, m_0, the number of controls, is many times larger than m_1, the number of cases.
Since it is known that in terms of statistical power a value of $k=m_0/m_1$ greater than three or four is seldom worthwhile (Gail et al, 1976), it was decided to reduce m_0 by taking a random sample of size m_0' from all survivors and to analyse the data in terms of a case-control study with m_1 cases and m_0' controls. This results in the following modified 2x2 table:

	F^+	F^-	
cases	a	b	m_1
controls	c'	d'	m_0'

where c' and d' are the numbers of controls in whom F is present and absent, respectively. From this reduced sample the odds ratio (3) can be estimated as:

$$\frac{ad'}{bc'} \qquad (5)$$

Because both the m_0 survivors and the m_0' controls are random samples from the survivors in the population, (5) and (4) are both estimators of the same parameter.

Since m_0' is a random sample from m_0 the expectation of c' is given by:

$$E(c') = \frac{m_0'}{m_0} c$$

and an unbiased estimate of c is:

$$\hat{c} = c' \frac{m_0}{m_0'}$$

With this result, the absolute risk of death for a patient having F can be estimated as:

$$P_1 = \frac{a}{a+c' \frac{m_0}{m_0'}}$$

In the present study, in which the control sample comprised 9% of the survivors, the number of patients for whom full baseline data had to be collected was reduced by about 4500 through the use of this design. Thus vast amounts of time and money were saved. Moreover, as more attention could be given to error checking, the quality of the data was greatly increased and the proportion of missing values was kept low.

2.5 Follow-up

Name, date of birth, sex and address of each patient were sent to the municipality under which his or her place of residence resorted. In The Netherlands these data are registered at the town hall for each person living in the municipality. Changes due to death or migration are carefully recorded.
From these local registries it was ascertained whether or not patients were still living at the same address. If so, the patient was recorded as living at the date of enquiry. This date was always at least 18 months after the date the ECG-recording took place. If the patient had died,

date and place of death were obtained, as well as the number of the death certificate. If a patient had moved, date and new address were obtained and the procedure was repeated with the new address. If a patient had moved to another country he or she was recorded as as living at the date of departure.

For some patients this procedure was not successful. In that case an attempt was made to contact the patient's general practitioner. Only 9 patients (.2%) could not be traced in any of these ways. These are not included in the 5130 patients mentioned in section 2.3.

The results were stored in a computer file containing for each patient: identification, sex, date of birth, date of ECG-recording and the date at which the patient had died or had been recorded alive. A binary variable indicated whether the latter date indicated a death or a survival. To this file was added the indication for ECG-recording as stated on the request form (see 2.2.2).

2.6 Selection of cases and controls

Cases were defined as patients who died within 18 months of 24-hour ECG-recording. Controls were randomly selected from all patients known to be alive 18 months after the date of ECG-recording. The sampling fraction (9%) was chosen to ensure that the number of controls would be at least twice the number of cases. The actual sampling procedure was as follows. Cards which represented all patients in the sample were ordered according to the hospital in which the patient was under treatment and per hospital according to date of ECG-recording. Cards representing either cases or patients with incomplete follow-up were removed. Nine cards were then drawn from each successive batch of 100 cards. These nine cards were chosen by means of a computer generated table of random numbers between 1 and 100.

2.7 Collection of baseline information for cases and controls

In addition to the information collected for all patients, the following extra baseline information was collected for cases and controls and stored in a computer file.

The semi-quantitative results of the analysis of the 24-hour ECG (see 2.2.4) were retrieved from the archives of Cardiolab. Use of drugs at time of ECG-recording was retrieved from the request forms (see 2.2.2). By means of a postal questionnaire, or by telephone in case of non-response, the referring physician was asked whether, at the time of the 24-hour ECG, in his or her opinion the patient had sustained a myocardial infarction, had angina pectoris or had had a pacemaker implanted. The date each event took place was asked in order to check that no events occurring after the ECG-recording were included. This also permitted the calculation of the time passed between the most recent myocardial infarction and ECG-recording (accurate to one month). If the physician who sent in the tape could not or would not answer the questions, the general practitioner was contacted. Only 5 cases and 7 controls had to be excluded because of lack of information.

For cases, the cause of death was asked on the questionnaire and was independently obtained from the physician who attended the patient at the time of death. This might or might not have been the same physician who answered the questionnaire.

A cardiologist, an epidemiologist and the author decided together, on the basis of all available information, whether a death should be classified as cardiac, non-cardiac or cardiovascular. Cardiac deaths included myocardial infarctions, arrhythmias and any kind of pump failure. Non-cardiac deaths were mainly carcinomas. The third group included cerebrovascular events and other causes directly or indirectly related to cardiovascular disease.

3 DATA ANALYSIS

This chapter describes the various statistical methods which were used to analyse the data collected. The estimation of the prevalence of patient characteristics in the sample from the observed prevalence among cases and controls is described in section 3.1, as well as the method which was used to explore possible relationships between indication and age. In section 3.2, three measures are described by which mortality was expressed. The definitions of different variables are given in section 3.3 together with some other points pertaining to univariate analysis. The basic approach of multivariate analysis is explained in 3.4.1 while 3.4.2 describes the method actually used for the selection of variables. Section 3.5 addresses the question of what can be learned from the equations resulting from multivariate analysis with regard to the prediction of mortality.
The sections of chapter 3 correspond to those of chapter 4. Section 3.1 describes the methods which led to the results in section 4.1, section 3.2 the methods which led to section 4.2 etc.
The interactive statistical computer program package SCSS (Nie et al, 1980) was used for data management and general computations.

3.1 Description of the sample

3.1.1 estimation of prevalence in the sample.

The prevalence of patient characteristics in the sample was estimated from the prevalence among cases and controls, as many characteristics which were known for cases and controls were not known for the total sample (see 2.5, 2.7). For this purpose, controls and cases were regarded as random subsamples from the two strata of patients who did or did not survive 18 months after ECG-recording. For controls this is true by definition (see section 2.6); for cases this is also true if we suppose that cases for whom information was lacking were randomly distributed over all cases, i.e. that there was no systematic influence which caused this information to be lacking. Patients who were lost to follow-up before 18 months had passed were disregarded for this analysis.

The fraction p_h of patients having a particular characteristic in stratum h (h=1,....,r where r is the total number of strata) is estimated by the corresponding fraction $\hat{p}_h$ in the subsample from that stratum. This estimate is subject to random error, as another random subsample from the same stratum may yield a different result. Therefore, a standard error of $\hat{p}_h$ is estimated as follows:

$$S(\hat{p}_h) = \sqrt{\frac{\hat{p}_h(1-\hat{p}_h)}{n_h}} \sqrt{1-\phi_h}$$

where n_h is the size of the subsample and ϕ_h the sampling fraction, which is equal to n_h/N_h with N_h the stratum size (Snedecor & Cochran, 1967). The finite population correction $\sqrt{1-\phi_h}$ is particularly necessary for the stratum of non-survivors because of the large sampling fraction. $S(\hat{p}_h)$ can be used to construct an approximate 95% confidence interval for p_h:

$$\hat{p}_h - 1.96\, S(\hat{p}_h) < p_h < \hat{p}_h + 1.96\, S(\hat{p}_h) \qquad (1)$$

The meaning of this confidence interval is, that if we were to take 100 random subsamples from the stratum, the true value p would be included in this interval 95 times.

The fraction of patients in the total sample (p_s) having a particular characteristic is estimated as a weighted average of the estimated fractions per stratum:

$$\hat{p}_s = \sum_{h=1}^{r} \frac{\hat{p}_h N_h}{N}$$

with $N=\Sigma N_h$. Because of the weighting, $\hat{p}_s$ is influenced more by the estimates $\hat{p}_h$ from larger strata. Similarly, the standard error of $\hat{p}_s$ is estimated as a weighted sum of the estimated standard errors per stratum:

$$S(\hat{p}_s) = \sqrt{W_h^2 \frac{\hat{p}_h(1-\hat{p}_h)}{n_h} (1-\phi_h)}$$

with $W_h=N_h/N$.

To estimate, for example, the proportion of patients without medication in the sample, we observe that $\hat{p}_h$ equals 25% for cases and 47% for controls (table 4.3/1) which (with N_1=213 and N_2=4882) gives 46% for $\hat{p}_s$. This is close to the proportion of controls because of the much greater size of the stratum of survivors. With n_1=195 and n_2=433 we find ϕ_1=.915 and ϕ_2=.089. $S(\hat{p}_1)$ is usually smaller than $S(\hat{p}_2)$ resulting in a narrower confidence interval for cases than for controls. Here $S(\hat{p}_1)=.9\%$ and $S(\hat{p}_2)=2.3\%$. $S(\hat{p}_s)=2.2\%$ which is again close to $S(\hat{p}_2)$. Using (1) this yields:

$$41.7\% < p_s < 50.3\%$$

When prevalences were not estimated in the total sample but in strata of e.g. age and sex, as in table 4.1/6, appropriate stratum and subsample sizes were used and these are given together with the estimates. Formula (1) is based on a normal approximation to the underlying binomial distribution. For small sample sizes and small values of p_h this approximation is inappropriate. Armitage (1971) gives a rule of thumb that it should not be used when the product $n_h\hat{p}_h$ is less than 10. Whenever a standard error for $\hat{p}_s$ is reported in chapter 4 based on $n_h\hat{p}_h<10$ in either of the strata, this is indicated by an asterisk.

3.1.2 relationships between indication and age

In order to explore possible relationships between indication and age, patients in the sample were assigned to mutually exclusive categories of age (10-year intervals) and indication. To do this, we devised a hierarchy of indications and a patient with more than one indication was treated as though the indication which was highest in this hierarchy was his or her only indication. A patient with the indication 'other' was excluded from other categories, as he or she may be suspected of having some unknown but important characteristics which might blur the relationship of interest. Similarly, when a pacemaker was involved, the patient was kept separate. A patient with dizziness and syncope was regarded as a patient with syncope, which seemed the more important of the two. A similar decision was made regarding patients with both myocardial infarction and coronary heart disease. Inspection showed that the age distribution of patients with palpitations and syncope and/or dizziness did not differ from the age distribution of patients with only the indication palpitations. These patients were therefore assigned to the palpitations category. For the same reason, patients with a myocardial infarction or coronary heart disease together with palpitations, syncope or dizziness were assigned to the category 'myocardial infarction' or 'coronary heart disease', respectively. 'Evaluation of therapy' and 'evaluation of arrhythmia' are rather unspecific indications and were therefore placed lowest in the hierarchy.

Thus, in descending order of importance, this hierarchy was as follows:

other
evaluation of pacemaker
myocardial infarction
coronary heart disease
palpitations
syncope
dizziness
evaluation of therapy
evaluation of arrhythmia

To the resulting two-way classification.the 'median polish' method was applied. In this technique, introduced by John W. Tukey (1977), a matrix of observations (O) is split into a matrix of estimated expectations (E) and a matrix of residuals (R) such that:

- O=E+R
- E is additive
- The median of the values in each row and each column of R is zero.

The additivity of E means that one row (column) follows from another row (column) by adding a constant to each element in that row (column). The elements of E can be regarded as the sum of three values: one peculiar to each row (row-effects), one peculiar to each column (column-effects) and one which is common for all elements of E (common value).
Deviations from this additive model appear in the matrix of residuals R.
Having computed E and R by either hand arithmetic or a suitable computer program (Gentle & Gregory, 1980; Velleman & Hoaglin, 1981; McNeill, 1977), one can then choose any element of E as the common value and compute row and column effects based on this value.
To check whether the additive model gives an adequate description of the data, residuals can be plotted against 'comparison values', which are defined as:

row-effect * column-effect / common value,

with the common median, i.e. the median of all elements of E, as common value.
If the model is not adequate, the slope of the line fitted to the resulting points indicates which data transformation may be used to improve it. Often, as in the application presented here, a log trans-

formation is an appropriate choice. This results in an additive model on log-scale which can be transformed back into a multiplicative model on the original scale. Calculations were done using the IMSL subroutine BEMDP (Gentle & Gregory, 1980).

3.2 Mortality in the sample

From the dates of ECG-recording and of death or recorded survival, the time of follow-up was computed for each patient in the sample. This information was used in three different ways.

Firstly, a survival curve was estimated using the method of Kaplan and Meier (1958). For each interval on the time axis the probability of survival was estimated as:

$$\frac{r_i - m_i}{r_i}$$

with m_i the number of deaths in the interval (t_i, t_{i+1}) and r_i the number of patients known to be alive at the beginning of that interval. This excludes patients who were lost to follow-up before t_i.

The probability P_i for a patient to be alive at time t_i is estimated as the product of the probabilities of survival in all intervals before t_i:

$$\hat{P}_i = \prod_{j=1}^{i-1} \left(\frac{r_j - m_j}{r_j}\right)$$

$\hat{P}_i$ can be interpreted as the estimated percentage of patients alive at t_i with censoring (i.e. the fact that patients are lost to follow-up before they reach the endpoint) taken into account.

To achieve a smooth curve, the length of the time-intervals in the present calculations was set to one week.

Secondly, the age- and sex-specific mortality in the sample was compared with the age- and sex-specific mortality in the Dutch population. For this purpose, four strata of age (in years) were defined: 10-44, 45-59, 60-69, 70 and over. This classification ensured that a sufficiently large number of deaths occurred in each stratum during both the first and the second year of follow-up. The numbers of patients at risk at the beginning of the first and second year of follow-up were counted in each age/sex stratum. For the Dutch population, the number of persons alive on January 1 1977 in each stratum was computed from figures provided by

the National Bureau of Statistics (CBS, 1978). The number of deaths per one thousand persons at risk in each stratum was computed from the observed number of deaths during the first year of follow-up and the year 1977 respectively. As suggested by Van der Maas and Habbema (1981), these were plotted against age to see how differences in mortality between the sample and the Dutch population varied with age.
To test the hypothesis whether the age- and sex-specific mortality rates in the sample are equal to those in the Dutch population, the number of deaths that could be expected in each stratum of the sample if this hypothesis were true was computed as death rate in the Dutch population times number of patients at risk in the stratum.
From the observed (O_i) and expected (E_i) number of deaths in the i-th stratum of the sample (i=1,...,k), the following test-statistic was computed:

$$X^2 = \sum_{i=1}^{k} \frac{(O_i - E_i)^2}{E_i}$$

which has approximately a chi-square distribution with k-1 degrees of freedom. This statistical test was applied separately to males and females in both the first and the second year of follow-up.
Thirdly, mortality in patients with different indications was compared. Because one patient might have several indications, a different measure of mortality was used here. Total follow-up time was accumulated for all patients with the same indication so that a patient who died 3 months after ECG-recording contributed .25 person-years and a patient who was lost to follow-up 2 years after ECG-recording contributed 2 person-years. When a patient had two indications his or her follow-up time contributed to both categories of indication.
The number of deaths per indication was divided by the total amount of person-years accumulated for that indication and multiplied by 1000, yielding a death rate per 1000 person-years of follow-up.

3.3 Description of cases and controls

Sections 2.5 and 2.7 describe the baseline information available for cases and controls. Except for age and for time passed since most recent previous MI, all variables were already dichotomous or were subsequently dichotomized. Categories of indication and medication (table 2.2/1), history of MI, history of angina, and pacemaker therapy were coded as present or absent. The semi-quantitative information on the occurrence of arrhythmias (see 2.2.4) was summarized by two variables. The first indicated presence or absence of the arrhythmia; the second indicated non-sporadic occurrence, i.e. in categories 2, 3 or 4 (see figure 3.3/1). Where appropriate, the second variable indicated 'continuous' occurrence, i.e. in category 4. Univariate distributions are given for all these variables for cases, for controls and, separately, for cases with a cardiac cause of death (see section 4.3).

3.3.1 odds ratio

Crude odds ratios were estimated from the absolute frequencies of patients in the four cells of the 2x2 table:

	F+	F−
cases	a	b
controls	c	d

as ad/bc. In this table a+b equals the number of (cardiac) cases and c+d equals the number of controls. As explained in section 2.4, the odds ratio is a good approximation to the relative risk if the risk of death is small, as is the case in the present study. Of course, every estimated odds ratio is subject to random error around the 'true' value it is supposed to estimate and it may be necessary to statistically test the hypothesis whether or not this odds ratio is different from unity. Such tests have not been applied here because they do not take into account possible confounding (i.e. a distortion of the association under conside-

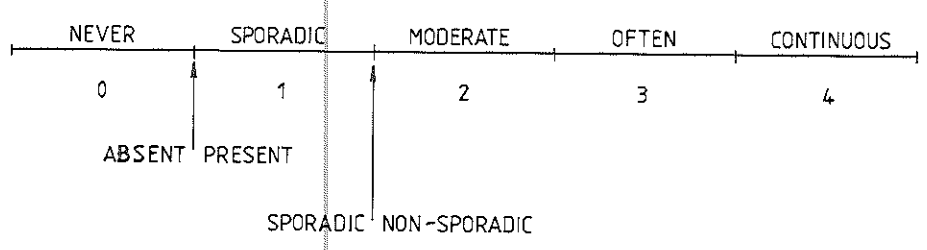


Figure 3.3/1
The frequency of arrhythmia occurrence was indicated on a 5-point scale (see 2.2.4). In the analysis, presence, non-sporadic occurrence and continuous occurrence were distinguished. Non-continuous occurrence is in categories 1,2 or 3.

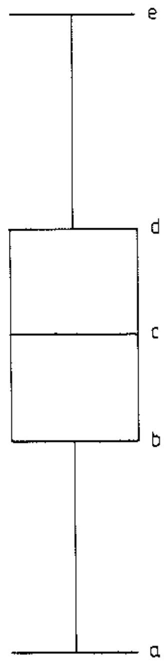


Figure 3.3/2
Example of a boxplot representing the quartiles of an empirical distribution. a=minimum, b=first quartile, c=median, d=third quartile, e=maximum.

ration brought about by a third variable – Breslow & Day, 1981; Matroos, 1981) and would therefore be meaningless. In the course of the multivariate analysis odds ratios are estimated which have been corrected for confounding and tests are applied there (see 3.4).

3.3.2 boxplots

The age distributions of cases and of controls with or without MI have been compared graphically by means of 'notched boxplots'. The 'boxplot' is an invention of J.W. Tukey (1977). It provides a graphical summary of an empirical distribution by indicating its quartiles and the distance between them (figure 3.3/2). Drawing several boxplots side by side is a useful means of comparing the distributions of one variable in several groups.
The notched boxplot (McGill, 1978) is a twofold extension of the original boxplot. Firstly, the width of the 'box' is made proportional to the square-root of the sample size (N). Secondly, an approximate 95% confidence interval around the median is indicated by 'notches'. This confidence interval is based on the interquartile range (R) as a robust measure of spread. It is computed as:

$$\text{median} \pm 1.58\ R/\sqrt{N}$$

Velleman and Hoaglin (1981) provide a theoretical justification for this formula.

3.4 Multivariate analysis

For any feature F_1 from the baseline data we can investigate possible association with mortality by estimating the odds ratio as described in 3.3.1. To avoid confounding of this estimate by a second feature F_2 it is possible to estimate the odds ratio of F_1 in several strata within which the value of F_2 is kept constant. An overall estimate can sub-

sequently be computed as a weighted average of the odds ratios in the individual strata (Mantel & Haenszel, 1959). When a third feature F_3 comes into play this procedure can be extended by constructing strata in which the values of both F_2 and F_3 are kept constant and so on for any number of variables.
However, when the number of possible confounders becomes large, the number of strata becomes unmanageable. For instance, for 10 dichotomous explanatory variables $2^{10} = 1024$ possible combinations exist and as many strata. Now it is evident that if sufficient information is to be present for the estimation of an odds ratio in all these strata, vast amounts of data will be needed. Also, one would have to ensure that the available data are evenly spread over all strata as otherwise there will be plenty of information in one stratum and none in another. Another drawback of this approach is that we can only investigate the association of one feature with mortality at a time. Estimation of odds ratios for different combinations of two or more variables simultaneously very quickly becomes impracticable.
The above limitations can be overcome when multivariate analysis is used. In the above approach the parameters to be estimated are the odds ratios and their number is equal to the number of strata.
In a multivariate approach the parameters to be estimated are the coefficients in a multiple logistic regression equation:

$$y = b_0 + b_1x_1 + b_2x_2, \ldots, b_kx_k$$

in which the x's are the variables of interest and possible confounders while

$$y = \ln \frac{P(D|X)}{1-P(D|X)} = \text{logit } P(D|X)$$

with $P(D|X)$ the probability of death within 18 months after ECG-recording given a particular combination of the x's.

For 10 variables of interest the situation of 1024 strata would correspond to a multivariate equation which contained 1024 x-variables, namely the 10 variables of interest as well as all possible interaction variables. Interaction variables are formed by multiplication of all possible combinations of two, three, four, etc., of the original ten variables. In such an equation, 1024 coefficients would have to be estimated and the odds ratio in one particular stratum would correspond to a unique combination of b's. In fact, b (or the sum of a number of b's) is the natural logarithm of the odds ratio as is easily seen when we consider that the natural logarithm of the odds ratio (the log odds) for a single feature

$$\ln \left(\frac{P(D|X_1)\ (1-P(D|X_1))}{P(D|X_0)\ (1-P(D|X_0))} \right) \qquad (2)$$

is equal to

$$\text{logit } P(D|X_1) - \text{logit } P(D|X_0) \qquad (3)$$

where X_1 is a combination of x's in which the variable x_r corresponding to that feature is of the value 1 and X_0 the same combination of x's with $x_r=0$.
Formula (3) is the subtraction of two multivariate equations yielding b_r as the result. Consequently the odds ratio in that stratum equals $\exp(b_r)$.
Rather than estimating 1024 coefficients, one attempts to reduce the number of coefficients to a manageable number by excluding most or all of the interaction variables from the equation. If all interaction variables were excluded, only the 10 variables of interest would remain and the number of parameters to be estimated would be reduced by 1014. The log odds in a particular stratum could then be estimated as a linear combination of the 10 coefficients in the equation. That is, the combination of x-values which characterizes a stratum could be inserted in the multivariate equation, leaving out the constant b_0, and the outcome computed. In section 3.5 it is explained how the constant b_0 can be used to compute logit $P(D|X)$, a transformation of the actual probability of death given the x-values rather than the odds ratio, which approximates the relative risk (see 2.4).
Of course, the odds ratios estimated in this way may be different from those estimated for each stratum separately. Discrepancies between the two can be inspected and tested for possible differences. This is called testing for goodness of fit. Estimating the odds ratios by means of the multivariate model also allows the estimation of odds ratios in strata in which no observations are available. Clearly, such estimates are meaningless when goodness of fit is inadequate.
In the present study, the coefficients in the two logistic regression equations have been estimated in two different ways. One is an application of linear discriminant analysis and was proposed by Cornfield (1961, 1962). In this approach the x-variables are assumed to be multivariate normally

distributed among both cases and controls with a common covariance matrix in the two groups. Though these assumptions are not satisfied here, this robust method can be used for an initial screening of variables (Breslow & Day, 1980, p. 204). The other method is known as the maximum likelihood method and has been proposed by Walker & Duncan (1967) and Day & Kerridge (1967). With the maximum likelihood method the above assumptions do not have to be made.

3.4.1 selection of variables

In the present analysis, four multiple logistic regression equations were constructed on the following variables:

- equation 1 : age, sex
- equation 2 : age, sex, clinical information except ECG-findings
- equation 3 : age, sex, ECG-findings
- equation 4 : age, sex, clinical information, ECG-findings

In equations 2 and 3, variables were selected after age and sex had been included in the equation. In equation 4, ECG-findings were selected after the variables of equation 2 had been included.
For the construction of each equation, all eligible variables were first screened for possible inclusion by means of interactive linear discriminant analysis (see above).
A variable was selected if the absolute value of the ratio of the estimated coefficient to the standard error of that estimate exceeded 1.96. For large numbers of patients in each group this test-statistic has approximately a standard normal distribution and this ratio is then called the z-value. The critical values chosen provided a two-sided test with a significance level of 5%. The coefficients in the equations which resulted from this procedure, were independently estimated by maximum likelihood (computer program by Lee, 1974). The same test-statistics were computed with the new estimates and variables which did not reach the significance level of 5% were again removed from the equation.

3.5 Calculations based on the multivariate equations found

3.5.1 estimation of risk from multivariate models

The multivariate logistic equations (see 3.4) are of the form:

$$\text{logit } P(D|X) = b_0 + b_1x_1 + b_2x_2,\ldots,b_kx_k \qquad (4)$$

where $x_1, x_2 \ldots x_k$ are the variables selected and $b_1, b_2 \ldots b_k$ are the

coefficients estimated for these variables. Knowing the values of the b's we can compute logit $P(D|X)$ for each patient from equation (4). This value may also be referred to as the sum-score (ss).
From the value of logit $P(D|X)$, $P(D|X)$ can be computed as:

$$P(D|X) = \frac{e^{ss}}{1 + e^{ss}}$$

However, a correction is necessary because the coefficients in the logistic equation have been estimated under the assumption that the prior probability of death (i.e. the death rate in the sample) equal to:

$$\frac{n_1}{n_1 + n_0}$$

with n_1 the number of cases and n_0 the number of controls on which the equation is based. This assumption is convenient from a computational point of view but incorrect. The correct formulation for the prior probability is:

$$\Pi_1 = \frac{n_1}{N}$$

in which N is the total number of patients of whom survival status was known at 18 months after ECG-recording. Anderson (1972) has shown that the b's in the equation are the same whatever the prior probability except for b_0, which needs to be corrected as follows:

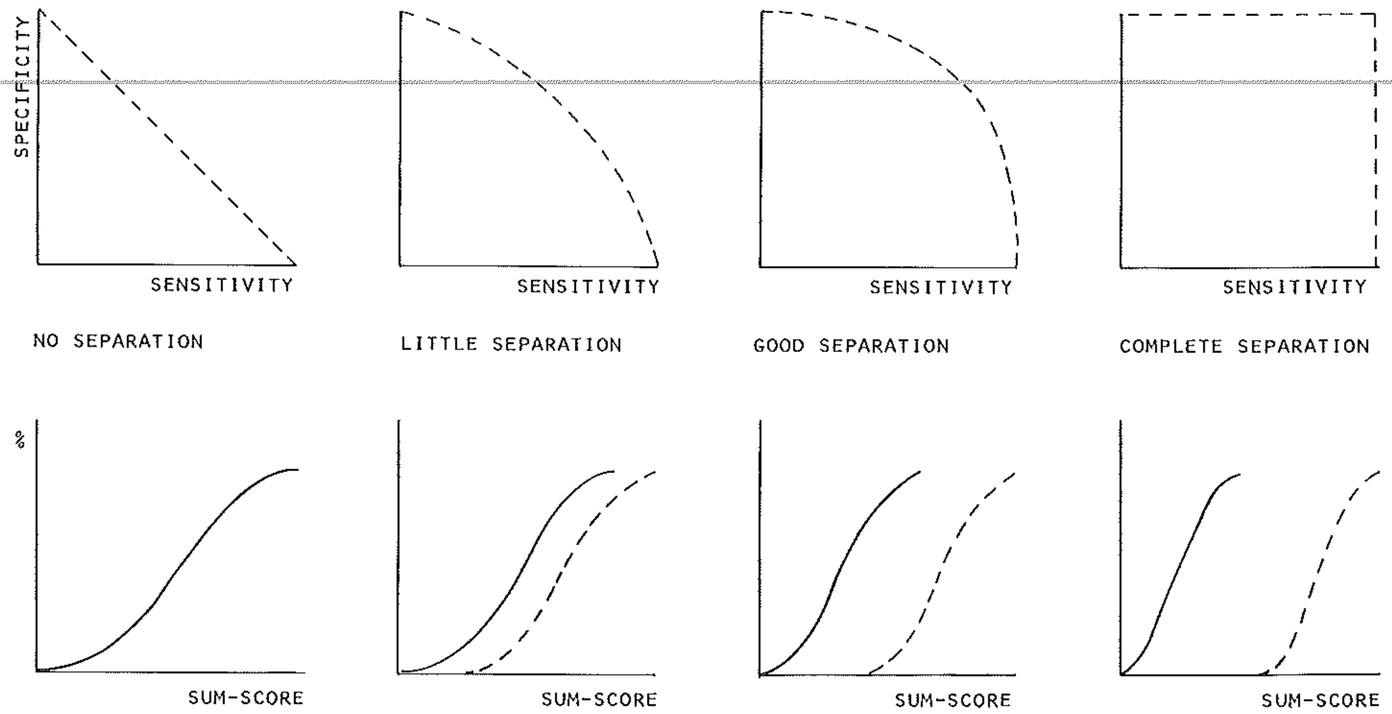
$$b_0' = b_0 + \ln \frac{n_0 \, \Pi_1}{n_1 \, \Pi_0}$$

where $\Pi_0 = 1 - \Pi_1$.
In the present study, $b_0'=b_0-2.402$ (taking $n_1=213$ and $N=5095$, see figure 4.3/1) when dealing with overall mortality and $b_0'=b_0-2.447$ ($n_1=123$) when dealing with cardiac mortality.

3.5.2 evaluation of the multivariate equations

With the formulas of section 3.5.1, the multivariate logistic equations can be used to estimate the probability of death within 18 months of ECG-recording for different categories of patients. The equations were also used to make a dichotomous prediction by taking an arbitrary cut-off point for $P(D|X)$ and comparing this to the actual value of $P(D|X)$ for a specific patient. For example a patient with $P(D|X) > 50\%$

Figure 3.5/1
Schematic representation of ROC curves.
Below: cumulative distribution of the sum-score for cases and controls. Above: the corresponding ROC curves.



may be predicted to die within 18 months while a patient with $P(D|X)<50\%$ may be predicted to survive. The cut-off value for $P(D|X)$ corresponds to a cut-off value for the sum-score. $P(D|X)=50\%$ corresponds to $\underline{ss}=0$, $P(D|X)=60\%$ to $\underline{ss}=0.4$, $P(D|X)=40\%$ to $\underline{ss}=-0.4$, etc.
Having computed the sum-score for each patient in the dataset of cases and controls, such a dichotomous prediction can be made for each of these patients and the following 2x2 table constructed:

	$\underline{ss} > ss$	$\underline{ss} \leq ss$
cases	a	b
controls	c	d

where ss is a chosen cut-off value of $\underline{ss}$.
Sensitivity (the proportion of correctly predicted cases) and specificity (the proportion of correctly predicted controls) can be computed as $a/(a+b)$ and $d/(c+d)$ respectively. These measures inform us about the quality of the prediction based on the cut-off value ss. Plotting specificity against sensitivity for several choices of $\underline{ss}$ yields a Receiver Operating Characteristic (ROC) curve (McNeill, 1975).
Comparison of the ROC curve with the two extreme situations (no predictive information is contained in the equation; the equation gives exact prediction) gives a visual impression of the performance of a multivariate logistic equation. The performance depends on the distributions of the sum-score for cases and controls respectively. The better the separation between the two distributions, the better the prediction that can be based on the equation from which the sum-scores were computed (figure 3.5/1). Because sensitivity and specificity have a scale which is independent of the distribution of the sum-score (which is unique to each equation), ROC curves can be used to compare the performance of different equations.

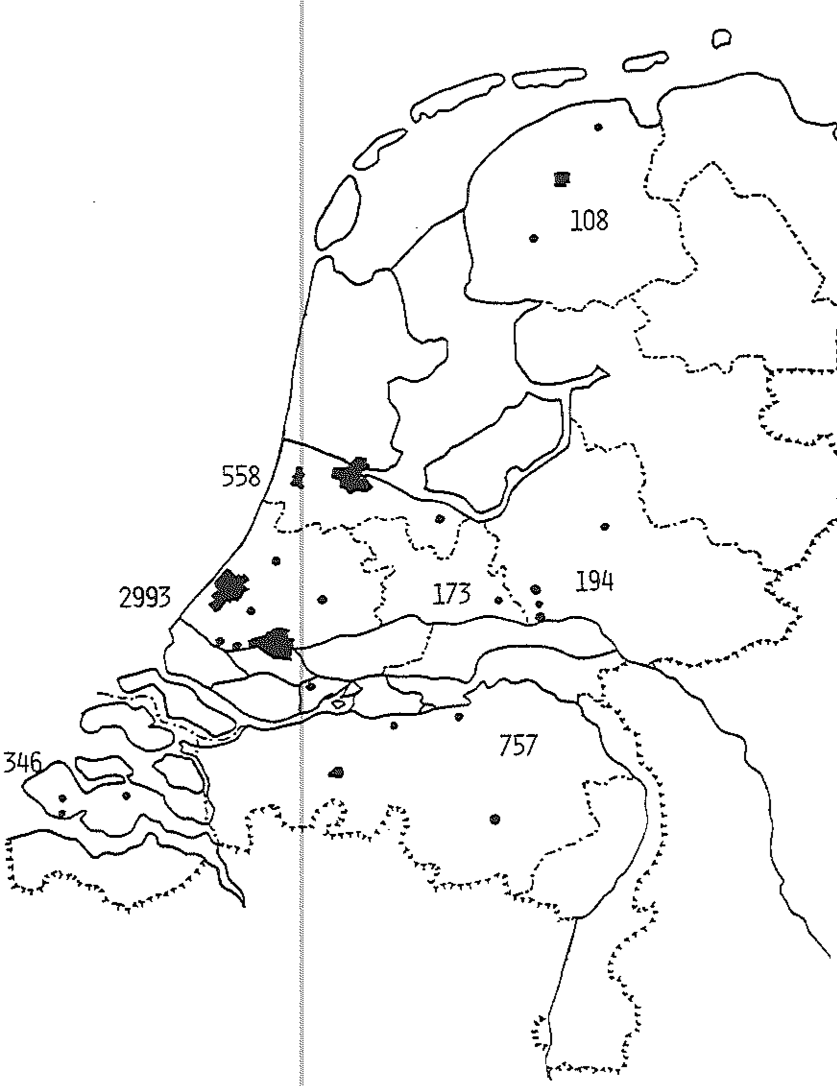


Figure 4.1/1
Distribution of patients in the sample over the 11 provinces of The Netherlands. The number of patients of whom a 24-hour ECG was recorded is indicated for each province. The towns shown are those in which one or more hospitals make use of the Cardiolab service.

4 RESULTS

4.1 Description of the sample

4.1.1 general description

The sample consisted of 5130 patients. Figure 4.1/1 shows how these patients were distributed over the 11 provinces of The Netherlands. The names of the 40 hospitals making use of the Cardiolab service during the period with which this study is concerned and the number of patients which each hospital contributed to the study are given in the appendix. Fifty-eight percent were male and median age (at the date of the 24-hour ECG) was 55 for males and 54 for females. Age distributions for males and for females in the sample are presented in figure 4.1/2. The distribution for males has a steeper slope which indicates a smaller spread.

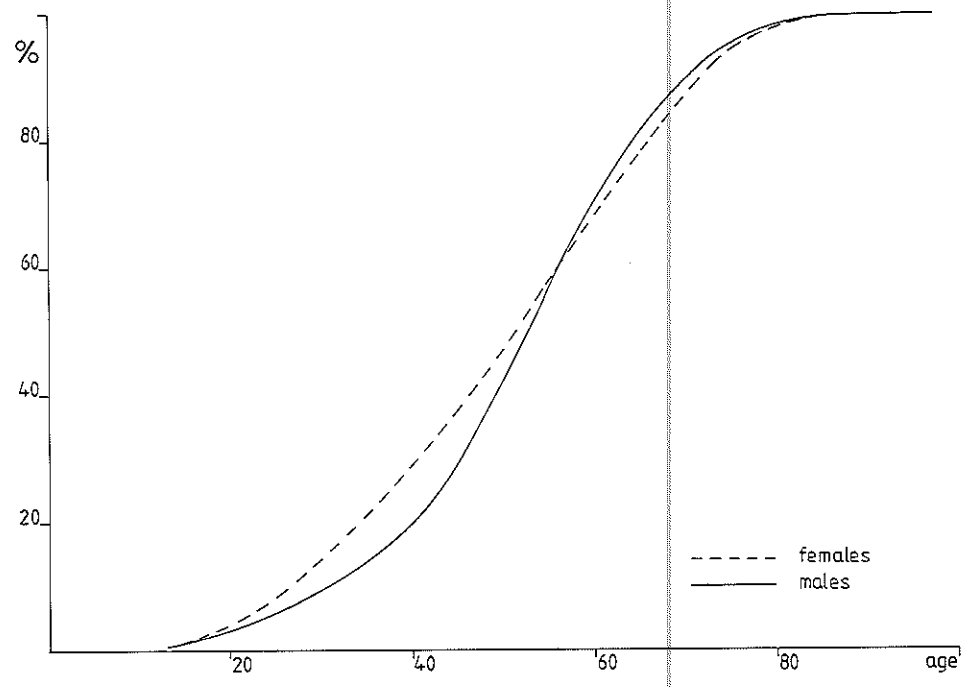


Figure 4.1/2
Age distributions of the 2962 males and 2168 females in the sample.

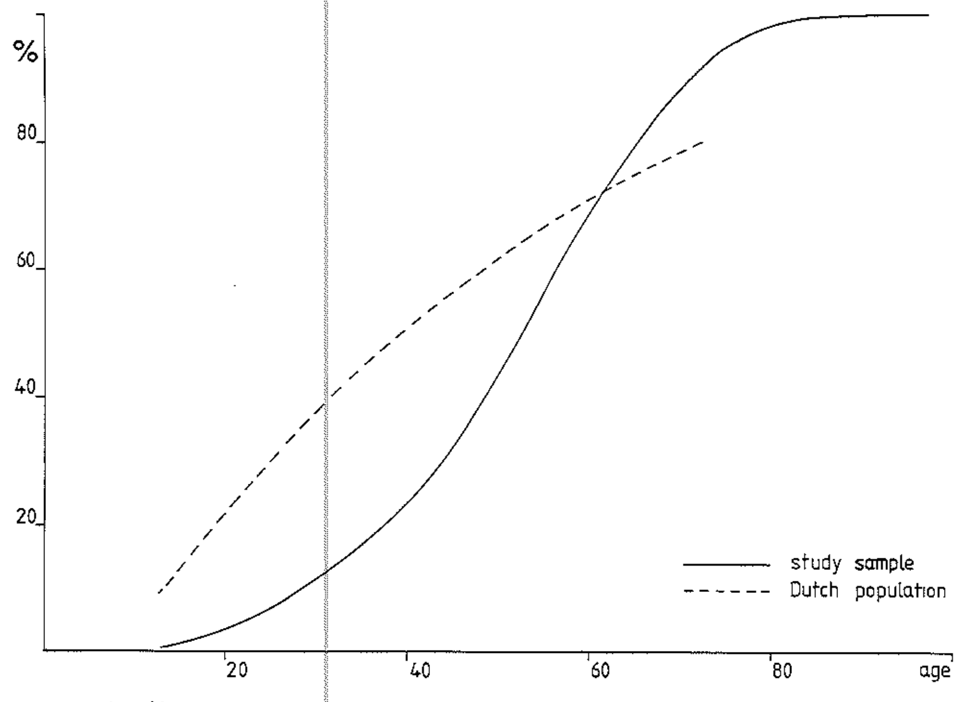


Figure 4.1/3
Age distributions of the 5130 patients in the sample and of the Dutch population (N=13,815,000) as recorded on January 1 1977.

A difference in slope is also the predominant feature when we compare (figure 4.1/3) the age distributions of the sample and of the Dutch population on January 1, 1977 (CBS, 1978). About 75% of the patients were aged between 40 and 70 years, while only about 30% of the Dutch population were in this range. Median age was 40 for the Dutch population and 55 for the sample.

Distributions for each sex of the indications as given on the request form (see 2.2.2) are shown in figure 4.1/4. The sum of the percentages for each sex exceeds 100 as patients may have more than one indication. 70% of patients had one indication, 23% had two, 5% had three or four, while 2% had no indication at all. The indications 'coronary heart disease', 'evaluation of therapy', 'evaluation of pacemaker' and 'other' each applied to less than 10% of patients. The indication 'palpitations' occurred substantially more often for females than for males, while the opposite was true of 'myocardial infarction' and 'evaluation of therapy'. Though indications were known for nearly all patients, more specific

Table 4.1/1

Estimated prevalence of history of myocardial infarction (MI) and angina pectoris (AP). Distribution of time interval between most recent MI and the 24-hour ECG in months.

		6% ⩽3 months
MI	21% (1.8%)	3% 3–12 months
		12% >12 months
		9% in combination with MI
AP	21% (1.8%)	12% not in combination with MI

% of sample (N=5130). Standard error of estimate in parentheses.

information was gathered from the referring physicians (see 2.7). On the basis of this information, the prevalence of myocardial infarction (MI) was estimated (see 3.1) to be 21% (table 4.1/1).
Even when taking into account the precision of this estimate, this figure was considerably higher than the relative frequency of the *indication* MI, which was 14% (as can be inferred from the marginal totals of table 4.1/3). This shows that a patient may well have sustained an MI, even if this is not indicated on the request form. Use of medication at the time of ECG-recording was retrieved from the request form for

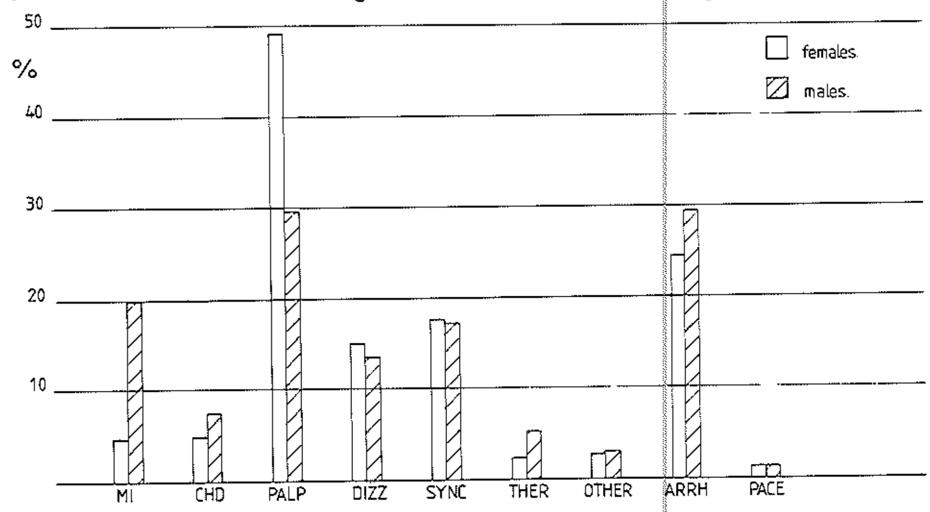


Figure 4.1/4
Distribution of indications for males and females.
Abbreviations see table 2.2/2.

Table 4.1/2
Estimated use of medication in the sample (N=5130).

	%	se
digitalis	11	1.3
diuretics	13	1.4
nitroglycerin	5	1.0
beta-blockers	16	1.6
anti-arrhythmics	17	1.6
anti-coagulants	6	1.0
other	22	1.8
none	46	2.2

se = standard error of estimate

cases and controls only. The estimated use of medication in the sample is shown in table 4.1/2. The category 'other' consisted mainly of patients taking sedatives. An estimated 46% of patients did not use any medication.

4.1.2 relationships between indication and age

In order to explore possible relationships between indication and age, patients were classified according to age and indication as described in section 3.1.2. The result is shown in table 4.1/3, with indications in descending order of 'importance'.

The 'median polish' method (see 3.1.2) was then used to fit a multiplicative model to these data. Given this model, the number of patients for each combination of indication and age (i.e. each cell of table 4.1/3) could be computed from the figures given in table 4.1/4, one for

Table 4.1/3
Numbers of patients in the sample classified according to indication and age

	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	TOTAL
OTHER	7	22	37	69	73	56	34	8	306
PACE	1	1	2	7	10	10	19	3	53
INF	0	4	24	109	238	203	84	6	668
CHD	1	1	13	51	110	73	31	1	281
PALP	40	184	274	350	399	280	128	18	1673
SYNC	17	30	42	76	144	173	154	51	687
DIZZ	3	23	31	41	71	80	70	27	346
THER	3	4	2	20	33	32	13	0	107
ARRH	28	83	115	165	230	175	105	23	924
TOTAL	100	352	540	888	1308	1082	638	137	5045

4 patients over 89 years of age and 81 patients for whom the indication was unknown have been excluded. Abbreviations see table 2.2/1.

Table 4.1/4
Multiplicative effects per indication, per category of age, and one common term

indication		age	
PALP	4.79	10-19	1.00
ARRH	2.75	20-29	1.78
SYNC	2.04	30-39	3.31
INF	1.05	40-49	8.71
DIZZ	1.00	50-59	10.00
OTHER	.91	60-69	10.00
CHD	.47	70-79	7.94
THER	.27	80-89	1.00
PACE	.12		

common term : 8.39

Abbreviations see table 2.2/1.

each indication, one for each age category and one which is common to all cells. For example the number of patients who were 40-49 and had the indication 'palpitations' is calculated under the model as: 8.39*8.71*4.79=350.
When the expected number of patients per cell is calculated using the figures in table 4.1/4 and displayed in a graph (figure 4.1/5) we find that the age distributions for different indications have the same form, though differing in magnitude. This is the natural consequence of assuming a multiplicative model.

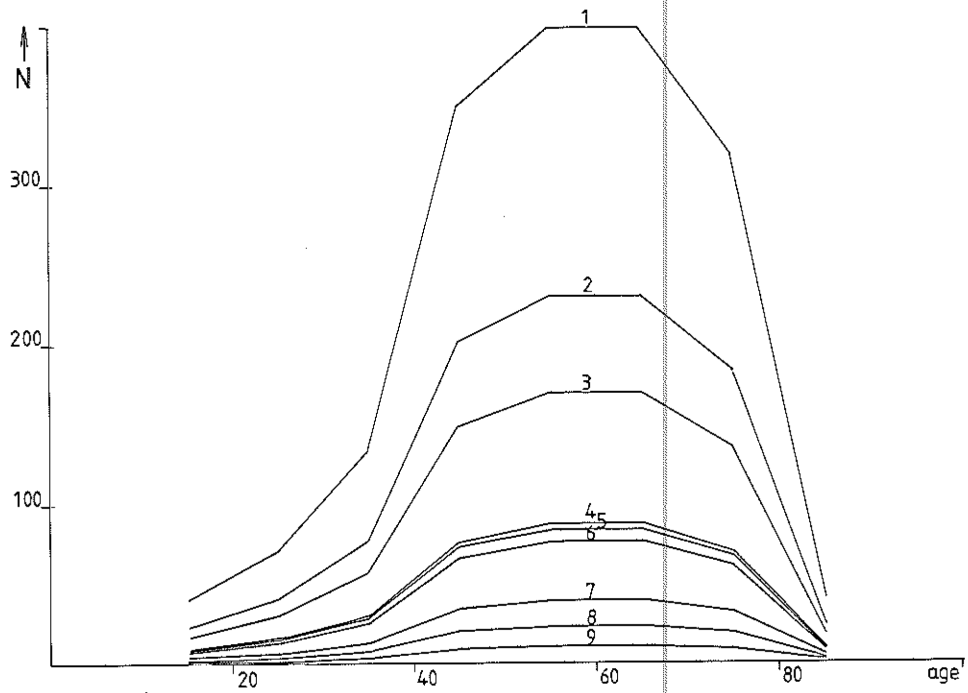
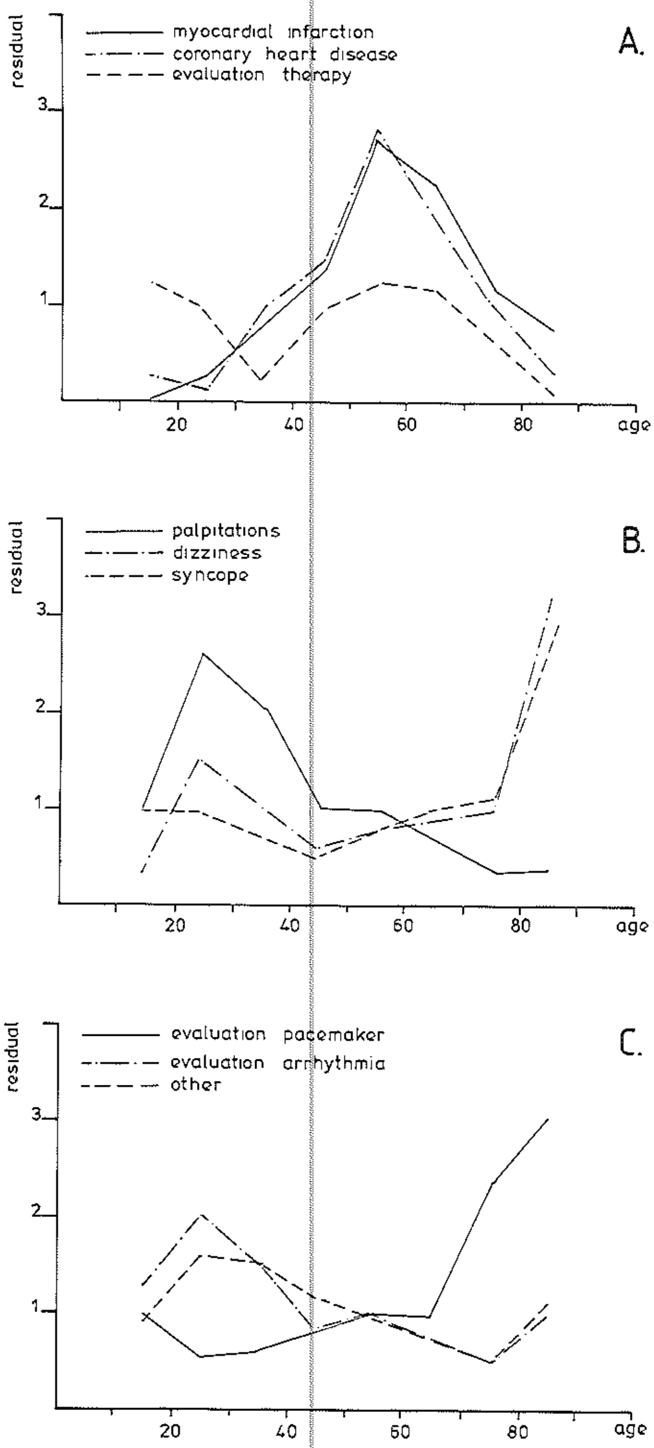


Figure 4.1/5
Number of patients by age for 9 categories of indication as estimated by multiplication of the effects given in table 4.1/4. 1=palpitations, 2=evaluation of arrhythmias, 3=syncope, 4=myocardial infarction, 5=dizziness, 6=other, 7=coronary heart disease, 8=evaluation of therapy, 9=evaluation of pacemaker.



residual
myocardial infarction
coronary heart disease
evaluation therapy
A.
3
2
1
20
40
60
80
age
residual
palpitations
dizziness
syncope
B.
3
2
1
20
40
60
80
age
residual
evaluation pacemaker
evaluation arrhythmia
other
C.
3
2
1
20
40
60
80
age

Figure 4.1/6
Residuals by age for each indication resulting from the application (on log-scale) of the 'median polish' to the matrix in table 4.1/3.

Patients are assumed to be spread over the age categories in a certain way regardless of their indication. If this assumption does not hold, this will become evident when the residuals are inspected.
We find the residual of each cell by dividing the observed number of patients by the expected number of patients. It is a measure of the dissimilarity between the expected number of patients per cell and the number actually observed. The more the residual differs from unity, the greater the dissimilarity between observed and expected numbers.
The residuals have been plotted against age (figure 4.1/6) for each indication. From figure 4.1/6A it is evident that large differences exist for the indications 'myocardial infarction' and 'coronary heart disease'. Patients with these indications in the age category 50-59 are nearly three times as numerous as the model specifies. Clearly, our supposition is not valid here; the actual age distributions of patients with MI or CHD have a different form than those of other patients.
Patients with MI or CHD are predominantly middle-aged (50-70) but are seldom in their twenties or in their eighties. Similarly, figure 4.1/6B suggests that patients with the indication 'palpitations' are younger than was assumed under the model. Patients with the indication 'evaluation of pacemaker' appear to be older than the model specifies (figure 4.1/6C).

Table 4.1/5
Sizes (in numbers of patients) of strata of age, sex and survival status of the available subsamples of cases and controls from those strata

	FEMALES			MALES			
	40	40-60	60	40	40-60	60	total
deaths	1	11	37	5	47	112	213
survivors	524	804	779	475	1349	951	4882
cases	1	8	35	5	45	101	195
controls	61	63	65	40	126	78	433

Table 4.1/6

Estimated prevalence of arrhythmias in 6 strata of age and sex

	FEMALES			MALES			
	40	40-60	60	40	40-60	60	total
Stratum size(=100%)	525	815	816	480	1396	1063	5095
	%	%	%	%	%	%	%(se)
No arrhythmias	13	10	2	8	6	0	6(1.0)*
Uniform PVCs	57	78	78	80	82	96	81(1.8)*
Multiform PVCs	18	40	60	30	53	71	49(2.2)
Bigeminy	7	11	20	8	20	19	16(1.6)
Doublets	16	16	33	5	28	43	26(1.9)
Short VT	5	3	6	2	12	23	10(1.3)
Long VT	0	0	0	0	1	5	1(0.4)*
PSVC	41	67	79	29	54	76	60(2.2)
SVT	7	13	37	5	13	31	18(1.7)
Sinus tachycardia	33	14	6	23	10	5	13(1.5)
Sinus bradycardia	5	19	14	30	11	17	15(1.6)
Atrial fibrillation	2	1	13	0	5	8	5(1.0)
Nodal rhythm	8	0	2	3	2	3	3(0.8)*
1° AV-block	5	3	4	0	5	5	4(0.9)
2° AV-block	0	3	3	3	5	5	4(0.9)*
IVCD	0	2	6	3	4	2	3(0.8)
Sinus arrest	5	5	12	17	7	5	8(1.2)
Short ventr. arrest	0	2	5	3	2	3	2(0.6)*
Long ventr. arrest	0	0	1	0	1	1	1(0.4)*
Pacemaker rhythm	0	0	5	0	1	1	1(0.4)*

* normal approximation not appropriate see 3.1.1

Abbreviations see table 2.2/2. se = standard error of estimate

Table 4.1/7

Estimated prevalence of arrhythmias in 6 strata of age and sex only considering non-sporadic or continuous occurrence

	FEMALES			MALES			
	40	40-60	60	40	40-60	60	total
Stratum size(=100%)	525	815	816	480	1396	1063	5095
non-sporadic	%	%	%	%	%	%	%(se)
Uniform PVCs	11	21	34	20	40	51	34(2.1)
Multiform PVCs	0	7	12	8	12	18	11(1.3)
Bigeminy	5	2	5	3	6	8	5(1.0)
Doublets	0	3	2	0	1	9	3(0.6)*
PSVC	10	18	29	3	11	26	17(1.7)
SVT	0	2	3	0	1	2	1(.4)*
continuous							
Atrial fibrillation	0	0	3	0	2	2	1(.4)*
1° AV-block	2	2	1	0	2	3	1(.4)*
IVCD	0	2	3	0	2	1	2(.6)*

* normal approximation not appropriate see 3.1.1

Abbreviations see table 2.2/2. se = standard error of estimate

4.1.3 prevalence of arrhythmias

By means of the procedures described in section 3.1.1, the prevalence of arrhythmias was estimated both in the total sample and in six strata of age and sex (tables 4.1/6,7). The sizes of the strata and of the samples from which the prevalences were estimated are given in table 4.1/5.
Ventricular arrhythmias were more often present in males and supraventricular premature complexes in females. There did not seem to be any difference for the remaining arrhythmias.
The ventricular arrhythmias, premature supraventricular complexes and supraventricular tachycardia occurred more frequently in higher age groups.

In addition to considering strata of age and sex, the prevalence of arrhythmias in several mutually exclusive categories of indication

Table 4.1/8

Estimated prevalence of arrhythmias among patients with the indication 'myocardial infarction'

	% (se)
Uniform PVCs	94 (2.8)*
Non-sporadic uniform PVCs	50 (5.8)
Multiform PVCs	74 (5.1)
Bigeminy	26 (5.0)
Doublets	42 (5.7)
Short VT	25 (4.9)
Long VT	3 (1.6)*

% of 668 patients with the indication
based on 62 out of 66 deaths and 55 out of 602 survivors
* normal approximation not appropriate see 3.1.1
Abbreviations see table 2.2/2. se = standard error of estimate.

Table 4.1/9

Estimated prevalence of arrhythmias among patients with the indication 'palpitations'

	% (se)	Short VT	7 (1.9)*
Uniform PVCs	72 (3.3)*	Long VT	0
Non-sporadic uniform PVCs	23 (3.0)	PSVC	58 (3.6)*
		SVT	15 (2.6)*
Multiform PVCs	33 (3.4)*	Sinus bradycardia	10 (2.2)*
Bigeminy	9 (2.1)*	Atrial fibrillation	5 (1.6)*
Doublets	15 (2.5)	Sinus tachycardia	20 (2.9)*

% of 1673 patients with the indication
based on 24 out of 28 deaths and 163 out of 1645 survivors
* normal approximation not appropriate see 3.1.1
Abbreviations see table 2.2/2. se = standard error of estimate

Table 4.1/10

Estimated prevalence of arrhythmias among patients with the indication(s) 'dizziness' and/or 'syncope'

brady-arrhythmias	% (se)	tachy-arrhythmias	% (se)
Sinus bradycardia	21 (9.2)*	VT	9 (2.8)*
1° AV-block	6 (2.5)*	SVT	20 (4.2)*
2° AV-block	3 (1.8)*	Sinus tachycardia	9 (3.0)*
Sinus arrest	4 (2.0)*	Atrial fibrillation with fast ventr.response	4 (2.0)*
Ventr. arrest (2-3 sec)	7 (2.5)*		
Ventr. arrest (>3 sec)	2 (1.0)*		
Atrial fibrillation with slow ventr.response	4 (1.8)*		

% of 1033 patients with the indication(s)
based on 38 out of 47 deaths and 78 out of 986 survivors
* normal approximation not appropriate see 3.1.1
Abbreviations see table 2.2/2. se = standard error of estimate

(constructed as described in section 3.1.1) was estimated. Results are presented here for the categories 'myocardial infarction', 'palpitations' and for 'dizziness' and 'syncope' taken together. For each indication, estimates are given of relevant arrhythmias only, i.e. of arrhythmias which may be expected to occur in patients with that indication.
Table 4.1/8 shows the prevalence of ventricular arrhythmias in patients with the indication 'myocardial infarction'. It was estimated that one half of these patients had non-sporadic uniform PVCs, that 75% had multiform PVCs and that as many as 25% had short ventricular tachycardia.
Patients with the indication 'palpitations' had a high prevalence of sinus tachycardia and supraventricular tachycardia (table 4.1/9) and patients with the indications 'dizziness' and/or 'syncope' had a high prevalence of supraventricular tachycardia and sinus bradycardia (table 4.1/10). Comparison with table 4.1/6 shows, however, that these figures are not higher than the prevalences in the sample as a whole.
Only 7 cases and 5 controls had the indication 'evaluation of pacemaker'. These numbers were too small to make reliable estimates of the prevalence of arrhythmias in this category.

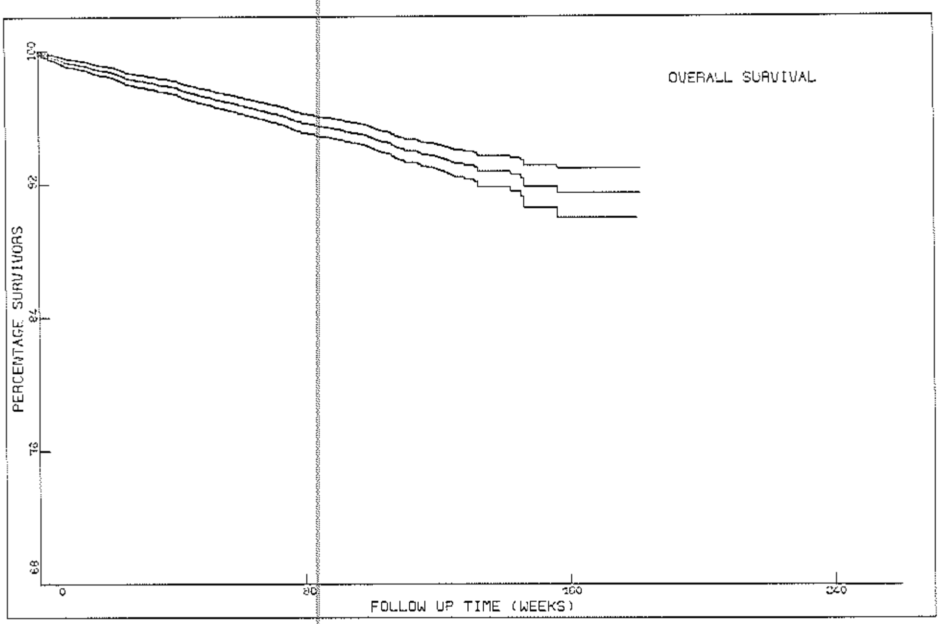


Figure 4.2/1
Percentage of survivors in the sample (N=5130) by time of follow-up and 95% confidence interval as estimated by the Kaplan-Meier method.

4.2 Mortality in the sample

Survival status was ascertained for 5130 patients. Time of follow-up after ECG-recording for survivors and non-survivors combined, ranged from less than one week to more than four years with a median of two years and three weeks. Three hundred and five patients died at varying time intervals after ECG-recording.

The percentage of patients alive at each week of follow-up was estimated through the method of Kaplan and Meier and displayed graphically in figure 4.2/1.

In order to compare the age- and sex-specific mortality in the sample with that in the Dutch population as a whole, the numbers of patients who had died during the first and second year of follow-up were counted in 4 strata of age for each sex separately (tables 4.2/1,2).
A total of 148 patients died during the first year of follow-up. Naturally, these patients were no longer at risk of death during the

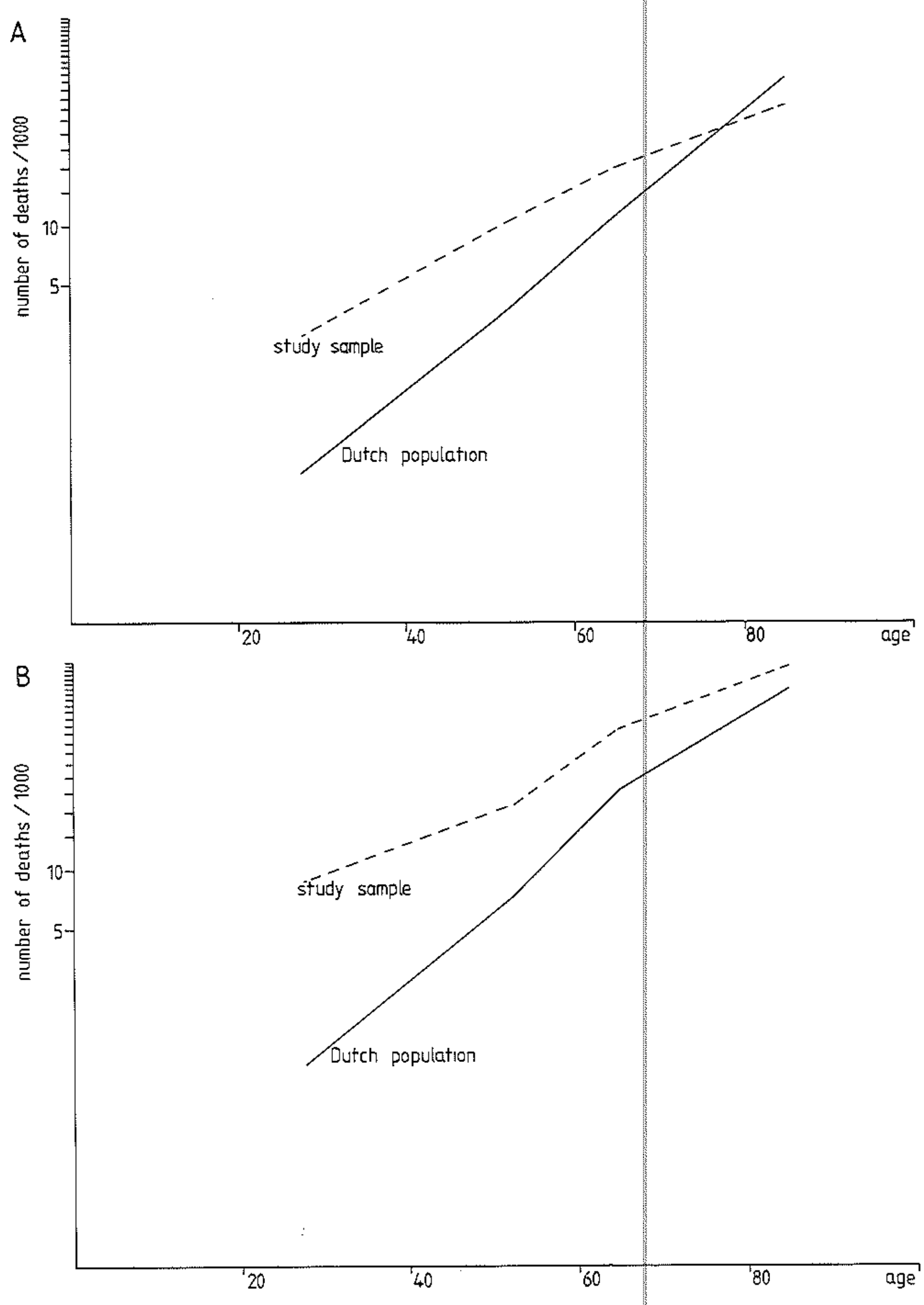


Figure 4.2/2
Observed number of deaths per thousand patients at risk during the first year of follow-up in the sample and during 1977 in the Dutch population in four strata of age (years). A: females, B: males.

Table 4.2/1

Comparison of mortality in the study sample and in the Dutch population during 1977. Females.

age (years)	patients at risk at t=0	observed deaths t=0-1	expected deaths t=0-1	patients at risk at t=1	observed deaths t=1-2	expected deaths t=1-2
10-44	710	2	.40	707	0	.40
45-59	640	7	2.53	632	8	2.50
60-69	439	9	5.14	430	5	5.04
≥70	379	16	22.01	363	15	21.08
total	2168	34	30.08	2132	28	29.02
X^2 (d.f.=3):		18.84 (P<.001)			14.25 (P<.01)	

t = time of follow-up after ECG-monitoring in years.

second year of follow-up, nor were the four survivors whose time of follow-up did not exceed one year. The numbers of patients at risk of death after one year are therefore also given in the tables.

The number of deaths per 1000 patients at risk during the first year was plotted against age (figures 4.2/2A,B) as was the number of deaths per thousand in the Dutch population during 1977 (CBS, 1978). At younger ages, mortality was considerably higher in the sample than in the Dutch population. This difference grew smaller with increasing age until for people who were 70 years or over mortality was nearly equal. Tables 4.2/1,2 show the number of deaths that would be expected in each stratum of the sample under the hypothesis that mortality per thousand is the same in the sample and in the Dutch population (see 3.2). Comparing observed and expected numbers of deaths, the same pattern which was evident in figure 4.2/2 was found in both the first and the second year of follow-up. From the values of the test-statistics in the tables it can be seen that, combining the information from the four strata of age, mortality rates are different in the sample from those in the Dutch population for both males and females and for both the first and second year of follow-up. However, differences were smaller for females than for males.

Table 4.2/2

Comparison of mortality in the study sample and in the Dutch population during 1977. Males.

age (years)	patients at risk at t=0	observed deaths t=0–1	expected deaths t=0–1	patients at risk at t=1	observed deaths t=1–2	expected deaths t=1–2
10–44	673	6	.70	667	8	.69
45–59	1218	27	8.54	1191	24	9.02
60–69	657	35	17.31	621	32	16.36
⩾70	414	46	35.33	367	29	31.32
total	2962	114	61.88	2846	93	57.39
X^2 (d.f.=3):		101.33 (P<.0001)			117.45 (P<.0001)	

t = time of follow-up after ECG-monitoring in years.

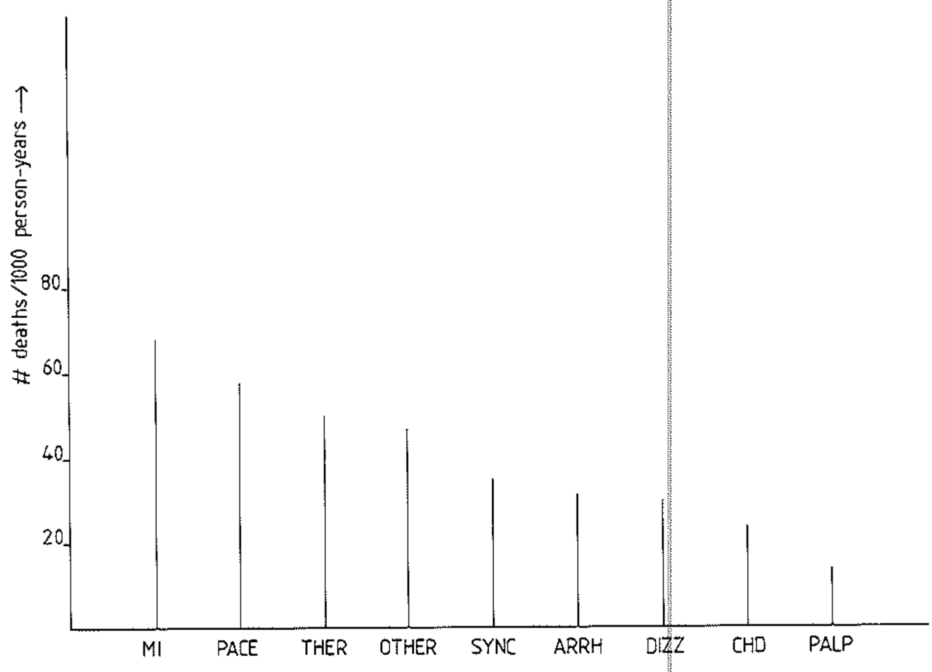


Figure 4.2/3
Number of deaths/1000 person-years of follow-up for nine categories of indication.

The observed number of deaths per 1000 person years of follow-up for each category of indication is shown in figure 4.2/3. Use of this measure permits comparison of categories of indication although they are not mutually exclusive. The indications have been ordered according to the mortality associated with them. In the sample, mortality was highest for MI and evaluation of pacemaker and lowest for palpitations and CHD.

4.3 Description of cases and controls

Cases were defined as patients who died within 18 months of ECG-recording. Survival status at 18 months after ECG-recording was not known for only 35 patients (.7%, figure 4.3/1). Of a total of 305 deaths (see 4.2), 213 satisfied the above definition. No baseline data were available for 18 cases; of 5 cases no information could be collected from the referring physician or general practitioner, while 13 cases were not followed up due to shortcomings in the administration or because they were detected too late. Four hundred and forty controls were randomly selected from 4882 patients who were known to be alive 18 months after the date of ECG-recording. Seven controls had to be excluded because of lack of information.

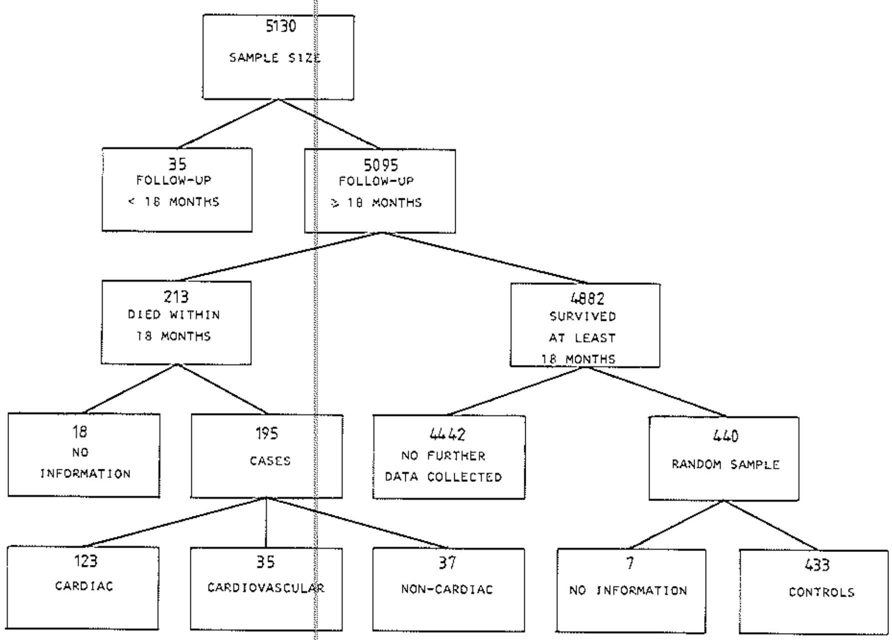


Figure 4.3/1
Tree diagram showing the sizes of different subsamples of patients

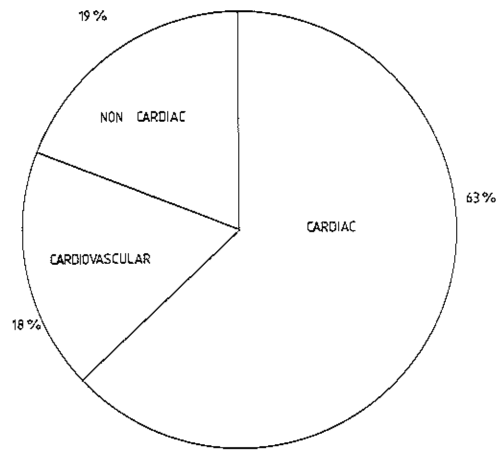


Figure 4.3/2
Distributions of causes of death over 195 cases.

Causes of death for cases were classified as cardiac, non-cardiac or cardiovascular (see 2.7). Figure 4.3/2 shows that two-thirds of cases died of a cardiac cause. Baseline data are presented here for the two subsamples comprising 195 cases and 433 controls, as well as for the 123 cases with a cardiac cause of death (tables 4.3/1,5). In addition, a division has been made between patients who sustained a myocardial infarction (MI) prior to ECG-recording (tables 4.3/2,6) and patients who did not (tables 4.3/3,7).

The age distributions of patients in different groups are presented in the form of notched boxplots (figure 4.3/3).

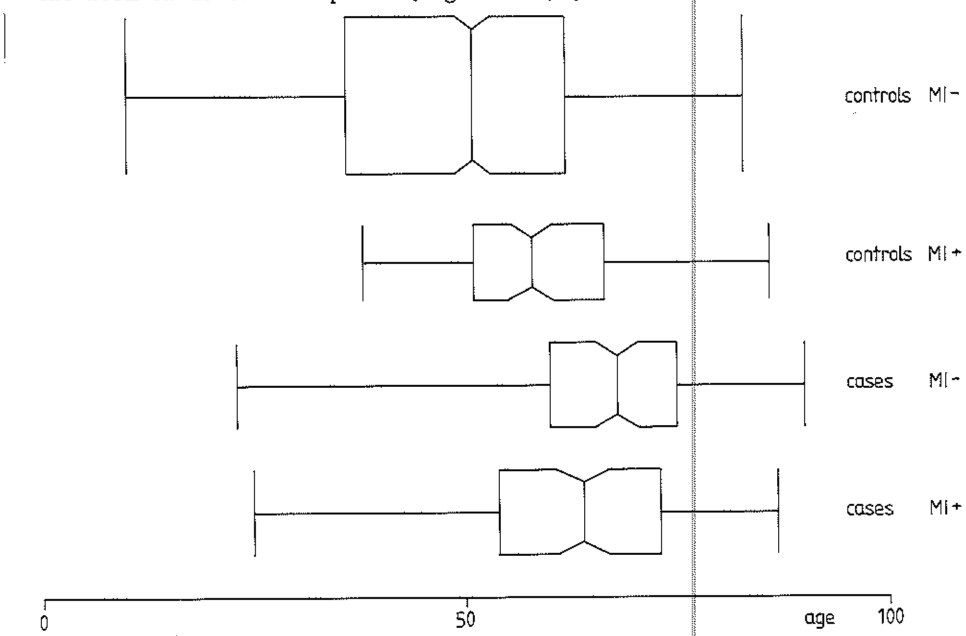


Figure 4.3/3
Notched boxplots showing the quartiles of the age distributions of cases and controls with and without MI. Width of box is proportional to group-size. Notches indicate 95% confidence intervals.

From these it is clear that controls are significantly younger than cases, though the age difference is smaller for patients with a prior MI than for those without.

Seventy-eight percent of cases were male but only 56% of controls (table 4.3/1). For patients with prior MI, this proportion was 87% in both subsamples (table 4.3/3). The indication 'myocardial infarction' occurred nearly three times more often in cases than in controls and most frequently in cases with a cardiac cause of death. The prevalence of prior MI which was reported by the physicians after specific questioning was almost 20% higher for cases than was apparent from the indications and was 7% higher for controls. From table 4.3/2 it can be seen that about 60% of prior MIs were reported on the request forms. For about 10 patients who had the indication 'myocardial infarction', the MI turned out to be insufficiently documented when the physician was specifically asked (table 4.3/3).

Of the other indications, 'palpitations' is particularly noteworthy because of the associated odds ratio, which is smaller than unity. It means that patients with this indication have a smaller risk of death than those without it (see 3.3). Of course, the odds ratios in these tables were not corrected for effects of age, sex, etc., and are therefore only a first approximation. The odds ratio associated with the indication 'evaluation of pacemaker' was one of the highest.
Of the medications, digitalis, diuretics and anti-coagulants had the highest odds ratios associated with them, reflecting the fact that these medications were used much more frequently among cases than among controls. The observation that the values of the corresponding odds ratios in table 4.3/2 are much smaller is caused by the fact that use of medication among controls with a prior MI was more prevalent than among those without a prior MI.

It is important to note that many odds ratios were higher when cardiac deaths were compared with survivors than when all deaths were considered. This means that the increased risk of non-cardiac or of cardiovascular death associated with the characteristic concerned is smaller than the associated risk of cardiac death and may even be non-existent (Cornfield et al, 1956; see also Breslow & Day, 1981).

Table 4.3/1

Univariate distributions of sex, history of MI, history of angina pectoris, pacemaker therapy, indication and medication for cases, controls and cases with a cardiac cause of death.

	cardiac cases	all cases	controls	OR cardiac	OR overall
number	123	195	433		
	%	%(se)	%(se)		
male sex	80	78(.9)	56(2.3)	3.1	2.7
myocardial infarction	66	54(1.0)	20(1.8)	7.9	4.7
MI within 3 months prior to ECG-recording	23	17(.8)	6(1.1)	4.8	3.5
angina pectoris	42	37(1.0)	20(1.8)	2.9	2.4
pacemaker	7	5(.5)*	2(.6)*	3.7	2.5
indication					
myocardial infarction	44	36(1.0)	13(1.5)	5.1	3.6
CHD	8	7(.5)	7(1.2)	1.2	1.0
palpitations	15	17(.8)	45(2.3)	.2	.3
dizziness	10	15(.7)	13(1.5)	.7	1.2
syncope	18	24(.9)	17(1.7)	1.1	1.5
evaluation of therapy	8	6(.5)	4(.9)	2.0	1.5
evaluation of arrhythmias	41	37(1.0)	26(2.0)	1.9	1.6
evaluation of pacemaker	5	4(.4)*	1(.5)*	4.4	3.2
other	10	11(.7)	6(1.1)	1.6	1.8
medication					
digitalis	37	34(1.0)	10(1.4)	5.2	4.5
diuretics	36	37(1.0)	12(1.5)	4.3	4.6
nitroglycerin	11	10(.6)	5(1.0)	2.3	1.9
beta-blocker	18	16(.8)	16(1.7)	1.2	1.1
anti-arrhythmics	36	29(.9)	16(1.7)	2.9	2.1
anti-coagulants	15	14(.7)	6(1.1)	3.0	2.7
other	29	32(1.0)	22(1.9)	1.7	1.5
none	22	25(.9)	47(2.3)	.3	.4

* normal approximation not appropiate see 3.1.1

OR = odds ratio. se = standard error of estimate

Table 4.3/2

Univariate distributions of sex, history of MI, history of angina pectoris, pacemaker therapy, indication and medication for (cardiac) cases and controls with a history of MI.

	cardiac cases	all cases	controls	OR cardiac	OR overall
number	81	105	85		
	%	%	%		
male sex	85	87	87	.9	.9
myocardial infarction	100	100	100	-	-
MI within 3 months prior to ECG-recording	35	32	30	1.3	1.1
angina pectoris	56	54	44	1.6	1.5
pacemaker	6	5	1	5.5	4.2
indication					
myocardial infarction	62	61	64	.9	.9
CHD	9	9	4	2.6	2.6
palpitations	10	12	20	.4	.6
dizziness	7	9	7	1.1	1.2
syncope	11	13	9	1.2	1.5
evaluation of therapy	11	10	8	1.4	1.2
evaluation of arrhythmias	41	40	37	1.2	1.2
evaluation of pacemaker	5	4	0	-	-
other	10	11	5	2.2	2.4
medication					
digitalis	38	37	19	2.7	2.5
diuretics	35	36	20	2.1	2.3
nitroglycerin	14	13	9	1.5	1.5
beta-blocker	20	17	18	1.1	1.0
anti-arrhythmics	42	38	37	1.3	1.1
anti-coagulants	19	17	19	1.0	.9
other	24	27	24	1.0	1.2
none	20	20	22	.9	.9

OR = odds ratio.

Table 4.3/3

Univariate distributions of sex, history of MI, history of angina pectoris, pacemaker therapy, indication and medication for (cardiac) cases and controls without a history of MI.

	cardiac cases	all cases	controls	OR cardiac	OR overall
number(=100%)	42	90	348		
	%	%	%		
male sex	69	67	49	2.3	2.1
myocardial infarction	0	0	0	-	-
MI within 3 months prior to ECG-recording	-	-	-	-	-
angina pectoris	17	18	14	1.2	1.3
pacemaker	10	6	2	4.5	2.5
indication					
myocardial infarction	10	7	1	9.1	6.1
CHD	7	4	7	1.0	.6
palpitations	24	22	51	.3	.3
dizziness	14	22	14	1.0	1.7
syncope	31	35	18	2.0	2.4
evaluation of therapy	2	2	3	.7	.7
evaluation of arrhythmias	41	33	24	2.2	1.6
evaluation of pacemaker	5	3	1	3.4	2.3
other	10	11	7	1.5	1.7
medication					
digitalis	36	31	8	6.1	4.9
diuretics	38	39	10	5.9	6.0
nitroglycerin	7	6	4	1.7	1.3
beta-blockers	14	15	15	.9	1.0
anti-arrhythmics	24	18	11	2.5	1.7
anti-coagulants	10	11	3	4.0	4.7
other	41	39	21	2.5	2.3
none	26	31	53	.3	.4

OR = odds ratio

Table 4.3/4
Numbers of patients in whom rare arrhythmias were detected

Idioventricular rhythm	8
Acc. idioventricular rhythm	1
Acc. nodal rhythm	4
Atrial flutter-normal VR	2
Atrial flutter-slow VR	0
Atrial flutter-fast VR	0
Ventricular fibrillation	1
Ventricular flutter	1
3° AV-block	5
SVT-block	7
WPW	2
Parasystole	2

Acc.=Accelerated
VR=ventricular response

A number of arrhythmias that were originally distinguished, occurred so infrequently in the 628 cases and controls with whom we are dealing here, that it was impossible to consider them in a systematic analysis (table 4.3/4). Other arrhythmias were combined in order to reach sufficient numbers. These included a) escape beats, combining nodal and ventricular escape beats, b) atrial fibrillation, where the ventricular frequency has been disregarded, c) second degree AV-block, comprising both Wenckebach and Mobitz patterns, d) ventricular tachycardia, which now denotes presence of either short or long ventricular tachycardia.

Table 4.3/5 contains two so-called 'composite variables'. Composite variables form a useful combination of variables already present in the table. They have been created in the process of variable selection and model building because of the need to

Table 4.3/5
Univariate distributions of arrhythmias for cases, controls and cases with a cardiac cause of death

	cardiac cases	all cases	controls	OR cardiac	OR overall
Number(=100%)	123	195	433		
	%	%(se)	%(se)		
No arrhythmias	1	2(.3)*	6(1.1)	.1	.3
ventricular					
Uniform PVCs	95	95(.5)	80(1.8)	5.0	4.7
Multiform PVCs	80	75(.9)	48(2.3)	4.3	3.3
Bigeminy	33	30(1.0)	15(1.6)	2.8	2.5
Doublets	57	53(1.0)	25(2.0)	3.9	3.3
VT	32	29(.9)	10(1.4)	4.4	3.9

Table 4.3/5 (continued)

	cardiac cases	all cases	controls	OR cardiac	OR overall
supraventricular	%	%(se)	%(se)		
PSVC	63	64(1.0)	60(2.2)	1.1	1.2
SVT	30	25(.9)	18(1.8)	2.0	1.5
Sinus bradycardia	15	11(.7)	15(1.6)	1.0	.7
Sinus tachycardia	4	3(.4)*	5(1.0)	.3	.2
Nodal rhythm	5	4(.4)*	3(.8)	2.0	1.4
Atrial fibrillation	15	16(.8)	5(1.0)	3.4	3.7
other					
1° AV-block	15	12(.7)	4(.9)	4.8	3.5
2° AV-block	6	4(.4)*	4(.9)	1.7	1.0
IVCD	15	11(.7)	3(.8)	6.0	4.2
Sinus arrest	7	6(.5)	8(1.2)	.8	.8
Ventr. arr.(2-3 sec)	7	7(.5)	2(.6)*	3.7	3.4
Ventr. arr.(>3 sec)	7	3(.4)*	1(.5)*	5.4	6.8
Escape beats	7	5(.5)*	2(.6)*	2.4	1.9
non-sporadic[1]					
Uniform PVCs	57	52(1.0)	32(2.1)	2.8	2.3
Multiform PVCs	37	25(.9)	11(1.4)	4.6	3.5
Bigeminy	13	10(.6)	5(1.0)	2.8	2.1
Doublets	17	13(.7)	3(.8)	7.9	5.9
PSVC	24	25(.9)	16(1.7)	1.6	1.7
SVT	6	6(.5)	1(.5)*	5.2	5.1
continuous[2]					
Atrial fibrillation	11	11(.7)	1(.5)*	11.0	10.9
1°AV-block	11	8(.6)	1(.5)*	8.4	5.9
IVCD	9	7(.5)	2(.6)*	6.0	4.3
composite variables					
D2VT	36	32(1.0)	10(1.4)	4.9	4.2
ESCNR	11	9(.6)	5(1.0)	2.3	1.7

* normal approximation not appropiate see 3.1.1

1 'non-sporadic' denotes occurrence during >10% of recording time, see 2.2.4

2 'continuous' denotes occurrence during >90% of recording time, see 2.2.4

Abbreviations see table 2.2/2. OR = odds ratio. se = standard error of estimate

Table 4.3/6
Univariate distributions of arrhythmias for (cardiac) cases and controls with a history of MI

	cardiac cases	all cases	controls	OR cardiac	OR overall
Number(=100%)	81	105	85		
	%	%	%		
No arrhythmias	1	1	1	1.1	.8
ventricular					
Uniform PVCs	95	95	96	.7	.7
Multiform PVCs	78	79	71	1.5	1.6
Bigeminy	31	32	25	1.4	1.5
Doublets	56	57	41	1.8	1.9
VT	31	35	19	1.9	2.3
supraventricular					
PSVC	68	68	58	1.6	1.5
SVT	25	24	19	1.4	1.3
Sinus bradycardia	17	14	20	.8	.7
Sinus tachycardia	5	4	5	1.1	.8
Nodal rhythm	5	5	1	4.4	4.2
Atrial fibrillation	9	9	1	7.9	7.9
other					
1°AV-block	14	10	4	4.3	3.2
2°AV-block	6	5	5	1.3	1.0
IVCD	14	12	5	3.2	2.6
Sinus arrest	4	5	5	.8	1.0
Ventr. arrest (2-3 sec)	3	3	0	-	-
Ventr. arrest (>3 sec)	3	2	0	-	-
Escape beats	3	3	0	-	-
non-sporadic[1]					
Uniform PVCs	60	60	52	1.4	1.4
Multiform PVCs	35	36	26	1.5	1.6
Bigeminy	15	14	7	2.3	2.0
Doublets	16	16	9	1.8	1.9
PSVC	23	22	11	2.6	2.4

Table 4.3/7

Univariate distributions of arrhythmias for (cardiac) cases and controls without a history of MI

	cardiac cases	all cases	controls	OR cardiac	OR overall
Number(=100%)	42	90	348		
	%	%	%		
No arrhythmias	0	2	7	-	.3
<u>ventricular</u>					
Uniform PVCs	95	94	76	6.5	5.6
Multiform PVCs	83	70	42	6.9	3.3
Bigeminy	36	28	12	3.9	2.7
Doublets	59	48	22	5.4	3.4
VT	33	21	7	6.5	3.4
<u>supraventricular</u>					
PSVC	52	58	60	.7	.9
SVT	41	26	18	3.1	1.7
Sinus bradycardia	10	7	13	.7	.5
Sinus tachycardia	2	1	16	.1	.1
Nodal rhythm	5	2	3	1.7	.8
Atrial fibrillation	26	24	6	5.8	5.2
<u>other</u>					
1°AV-block	19	9	1	6.1	3.9
2°AV-block	5	2	3	1.5	.7
IVCD	17	10	2	8.5	4.7
Sinus arrest	12	8	9	1.4	.9
Ventr. arrest (2-3 sec)	17	11	3	7.5	4.7
Ventr. arrest (>3 sec)	2	4	1	4.2	8.0
Escape beats	14	8	3	4.7	2.3
<u>non-sporadic</u>[1]					
Uniform PVCs	52	44	28	2.9	2.1
Multiform PVCs	41	24	8	8.4	3.9
Bigeminy	10	7	5	2.2	1.5
Doublets	19	10	1	27.1	12.6
PSVC	24	28	18	1.4	1.7

Table 4.3/6 (continued)
patients with a history of MI

	cardiac cases	all cases	controls	OR cardiac	OR overall
continuous[2]	%	%	%		
Atrial fibrillation	4	4	0	-	-
1°AV-block	9	7	4	2.6	2.0
IVCD	10	9	4	3.0	2.6
composite variables					
D2VT	35	39	21	2.0	2.4
ESCNR	7	8	1	6.7	6.9

1 'non-sporadic' denotes occurrence during >10% of recording time, see 2.2.4
2 'continuous' denotes occurrence during >90% of recording time, see 2.2.4
Abbreviations see table 2.2/2. OR = odds ratio

summarize the available predictive information in as few variables as possible. D2VT denotes the occurrence of non-sporadic doublets and/or the presence of ventricular tachycardia. ESCNR indicates the presence of escape beats and/or nodal rhythm. The interpretation of both these variables is clear, as doublets and ventricular tachycardia are only distinguished by the number of PVCs in a sequence and nodal rhythm may well be an escape mechanism.

Ventricular arrhythmias generally occurred more frequently among cases than among controls (table 4.3/5). For patients with a prior MI these differences were smaller, due to a higher prevalence of ventricular arrhythmias among survivors with a prior MI as compared with survivors without a prior MI (table 4.3/6).

Supraventricular premature complexes appeared to be slightly more prevalent in cases with a prior MI than in other groups. Supraventricular tachycardia was consistently more prevalent in cases than in controls. Sinus bradycardia, on the other hand, was more prevalent in controls than in cases, resulting in odds ratios smaller than unity. Atrial fibrillation was clearly more prevalent in cases than in controls. This was also true for first degree AV-block and IVCD. The remaining arrhythmias occurred so infrequently that it was difficult to determine any differences between groups.

Table 4.3/7 (continued)

patients without a history of MI

	cardiac cases	all cases	controls	OR cardiac	OR overall
continuous[2]					
Atrial fibrillation	26	20	1	24.3	16.9
1°AV-block	14	9	1	19.2	11.1
IVCD	7	4	1	6.6	4.0
composite variables					
D2VT	38	24	8	7.6	3.9
ESCNR	19	10	6	3.5	1.6

1 'non-sporadic' denotes occurrence during >10% of recording time, see 2.2.4

2 'continuous' denotes occurrence during >90% of recording time, see 2.2.4

Abbreviations see table 2.2/2. OR = odds ratio

4.4 Multivariate analysis

All variables listed in tables 4.3/1 and 4.3/6 have been considered for the multivariate analyses, for which the results are reported in this section.

With two exceptions, these were all dichotomous variables indicating either presence or absence of an arrhythmia or other characteristic or else non-sporadic or continuous occurrence of an arrhythmia (see 3.3).

Patient age and the time interval between most recent previous MI and ECG-recording were coded in years and months respectively.

When continuous occurrence of an arrhythmia was indicated, the variable indicating presence or absence of that arrhythmia in table 4.3/6 was substituted for a variable indicating intermittent occurrence (i.e. in categories 1, 2 or 3, see 2.2.4), so that the relative importance of intermittent and continuous occurrence could be compared.

Following the procedure described in section 3.4.2, four multiple logistic regression equations were constructed.

Equation 1: age, sex

Equation 2: age, sex, clinical information except ECG-findings

Equation 3: age, sex, ECG-findings

Equation 4: age, sex, clinical information, ECG-findings

Table 4.4/1

Estimated coefficients (b) and test-statistics (Z) of multiple logistic regression equations for the prediction of cardiac mortality and overall mortality.

Equation 1: age and sex as the only variables.

	$b_{cardiac}$	$b_{overall}$	$Z_{cardiac}$	$Z_{overall}$
age (years)	.064	.073	7.04	8.96
sex (1=male,0=female)	1.188	1.046	4.56	4.80
constant	-5.787	-5.777	-9.242	-10.45

These equations were constructed separately for the prediction of cardiac mortality and overall mortality. The coefficients of the four equations, which were estimated by the maximum likelihood method, are given for both analyses in tables 4.4/1-4.

As other variables were entered into the equation, the coefficients of age and sex became smaller, indicating a positive correlation between these variables and age and sex.

Table 4.4/2

Estimated coefficients (b) and test-statistics (Z) of multiple logistic regression equations for the prediction of cardiac mortality and overall mortality.

Equation 2: age, sex and clinical information but not ECG-findings.

	$b_{cardiac}$	$b_{overall}$	$Z_{cardiac}$	$Z_{overall}$
age (years)	.052	.061	5.11	6.95
sex (1=male,0=female)	.796	.670	2.62	2.66
MI*	1.527	.972	6.05	4.40
palpitations*	-	-.586	-	-2.33
digitalis*	1.015	.861	3.41	3.26
diuretics*	.722	.833	2.33	3.19
constant	-5.856	-5.393	-8.35	-8.67

* 1=present,0=absent

Table 4.4/3

Estimated coefficients (b) and test-statistics (Z) of multiple logistic regression equations for the prediction of cardiac mortality and overall mortality.

Equation 3: age, sex and ECG-findings.

	$b_{cardiac}$	$b_{overall}$	$Z_{cardiac}$	$Z_{overall}$
age (years)	.051	.063	5.24	7.44
sex (1=male,0=female)	1.048	.987	3.62	4.16
multiform PVCs§	.793	.511	2.69	1.91
doublets§ and/or VT*	.759	.708	2.53	2.66
sinus bradycardia*	-	-.712	-	-2.11
SVT§	1.398	1.350	2.01	2.11
atrial fibrillation+	2.020	1.899	3.45	3.54
1° AV-block+	2.294	1.875	3.93	3.30
IVCD'	1.379	-	1.90	-
escape beats*	1.129	.965	2.54	2.22
constant	-5.631	-5.604	-8.48	-9.71

* 0=absent,1=present

§ 0=absent or present in category 1, 1=present in categories 2,3 or 4

\+ 0=absent,1=present in category 4

' 0=absent,1=present in categories 1,2 or 3

Abbreviations see table 2.2/2

For myocardial infarction (MI), as determined from interviews with the referring physicians, the estimated coefficient (b) was larger when predicting cardiac death than for the prediction of overall mortality. The same is true of the odds ratio (see 2.4) for MI, which is estimated from the equation as e^b. The odds ratio thus estimated from a particular equation is corrected for possible confounding by all other variables included in it.

Information about time passed since most recent previous MI did not contribute to prediction once the presence of a previous MI had been accounted for.

When considering overall mortality, the coefficient for palpitations was

Table 4.4/4

Estimated coefficients (b) and test-statistics (Z) of multiple logistic regression equations for the prediction of cardiac mortality and overall mortality.

Equation 4: age, sex, clinical information and ECG-findings.

	$b_{cardiac}$	$b_{overall}$	$Z_{cardiac}$	$Z_{overall}$
age (years)	.046	.057	4.28	6.19
sex (1=male,0=female)	.470	.606	1.42	2.27
MI*	2.059	1.165	6.79	4.78
palpitations*	-	-.565	-	-2.12
digitalis*	.891	.792	2.84	2.79
diuretics*	-	.708	-	2.58
doublets§ and/or VT*	.730	.634	2.33	2.33
sinus bradycardia*	-	-1.104	-	-3.04
SVT§	1.686	1.579	2.41	2.40
atrial fibrillation+	2.655	1.795	4.11	3.10
1° AV-block+	2.248	1.797	3.74	3.15
IVCD'	1.670	-	2.17	-
escape beats*	1.701	1.008	3.38	2.09
constant	-5.997	-5.443	-7.97	-8.28

* 0=absent,1=present

§ 0=absent or present in category 1, 1=present in categories 2,3 or 4

\+ 0=absent,1=present in category 4

' 0=absent,1=present in categories 1,2 or 3

Abbreviations see table 2.2/2

significantly smaller than zero. This indicates that patients with palpitations have a smaller risk of death than patients without this indication. The odds ratio for palpitations was estimated from equation 2 (table 4.4/2) to be 0.56. This variable made no contribution to the prediction of *cardiac* death, however.

When ECG-findings were added to age and sex, seven arrhythmias were found to contribute to the prediction of cardiac death (equation 3, table 4.4/3). Of these, two were ventricular arrhythmias, two were

supraventricular arrhythmias and three were due to abnormalities of impulse conduction or excessively slow impulse formation.
The same arrhythmias as well as sinus bradycardia but not intermittent IVCD contributed to the prediction of overall mortality.
When it was considered whether ECG-findings retained their prognostic significance when basic clinical information was first taken into account (equation 4), most of the arrhythmias of equation 3 were still found to contribute to the prediction. An exception was 'non-sporadic multiform PVCs' which was positively correlated with MI and therefore made no independent contribution once the presence of MI was accounted for in the equation. Similarly, 'use of diuretics' no longer contributed to the prediction of cardiac death because of its positive association with ventricular arrhythmias.
The coefficients of the arrhythmias were of the same order of magnitude in equations 3 and 4.

A further step in the analysis was to divide the subsamples of cases and controls into patients with and without MI. New coefficients for all variables selected for the prediction of cardiac death in the entire data set were estimated in each group separately, again considering cardiac deaths only. The results for equations 1-4 are presented in tables 4.4/5-8.
Naturally, the variable MI itself was not included as it had the same value for all patients in one group. For patients with a history of MI, no coefficient could be estimated by means of the maximum likelihood method for the variable 'continuous atrial fibrillation', because this

Table 4.4/5
Estimated coefficients (b) and test-statistics (Z) of a multiple logistic regression equation for the prediction of cardiac death in patients with (+) or without (-) myocardial infarction (MI).
Equation 1: age and sex as the only variables.

	b_{MI+}	b_{MI-}	Z_{MI+}	Z_{MI-}
age (years)	.027	.084	1.89	5.60
sex (1=male,0=female)	.040	1.006	.09	2.65
constant	-1.711	-7.661	-1.65	-7.288

Table 4.4/6

Estimated coefficients (b) and test-statistics (Z) of a multiple logistic regression equation for the prediction of cardiac death in patients with (+) or without (-) myocardial infarction (MI).

Equation 2: age, sex and clinical information but not ECG-findings.

	b_{MI+}	b_{MI-}	Z_{MI+}	Z_{MI-}
age (years)	.023	.075	1.59	4.73
sex (1=male,0=female)	.241	1.094	.50	2.58
digitalis*	.808	1.293	2.03	2.94
diuretics*	.356	1.118	.88	2.49
constant	-1.977	-7.682	-1.85	-6.92

* 1=present,0=absent

Table 4.4/7

Estimated coefficients (b) and test-statistics (Z) of a multiple logistic regression equation for the prediction of cardiac death in patients with (+) or without (-) myocardial infarction (MI).

Equation 3: age, sex and ECG-findings.

	b_{MI+}	b_{MI-}	Z_{MI+}	Z_{MI-}
age (years)	.027	.055	1.79	3.35
sex (1=male,0=female)	.160	.633	.32	1.37
multiform PVCs§	.187	1.203	.49	2.35
doublets§ and/or VT*	.532	.935	1.34	1.74
SVT§	1.565	1.317	1.29	1.42
atrial fibrillation+	-	2.782	-	4.07
1° AV-block+	1.266	3.110	1.74	3.28
IVCD'	.915	2.203	.72	2.34
escape beats*	2.126	1.624	1.86	2.66
constant	-2.238	-6.903	-1.99	-6.16

* 0=absent,1=present

§ 0=absent or present in category 1, 1=present in categories 2,3 or 4

\+ 0=absent,1=present in category 4

' 0=absent,1=present in categories 1,2 or 3

Abbreviations see table 2.2/2

Table 4.4/8
Estimated coefficients (b) and test-statistics (Z) of a multiple logistic regression equation for the prediction of cardiac death in patients with (+) or without (-) myocardial infarction (MI).
Equation 4: age, sex, clinical information and ECG-findings.

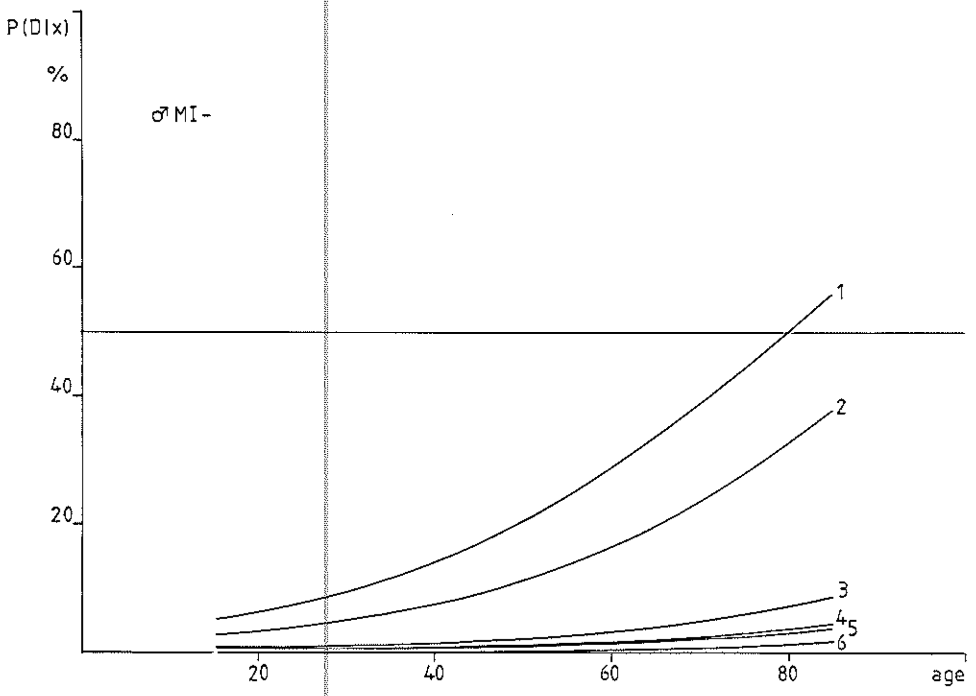
	b_{MI+}	b_{MI-}	Z_{MI+}	Z_{MI-}
age (years)	.026	.061	1.69	3.71
sex (1=male, 0=female)	.244	.498	.48	1.08
digitalis*	.858	1.171	2.26	2.21
doublets§ and/or VT*	.547	1.281	1.44	2.46
SVT§	1.164	1.598	.94	1.84
atrial fibrillation+	-	2.456	-	3.42
1° AV-block+	1.271	3.083	1.73	3.39
IVCD'	.883	2.082	.70	2.23
escape beats*	2.093	1.533	1.79	2.43
constant	-2.410	-7.173	-2.117	-6.31

* 0=absent, 1=present
§ 0=absent or present in category 1, 1=present in categories 2,3 or 4
\+ 0=absent, 1=present in category 4
' 0=absent, 1=present in categories 1,2 or 3
Abbreviations see table 2.2/2

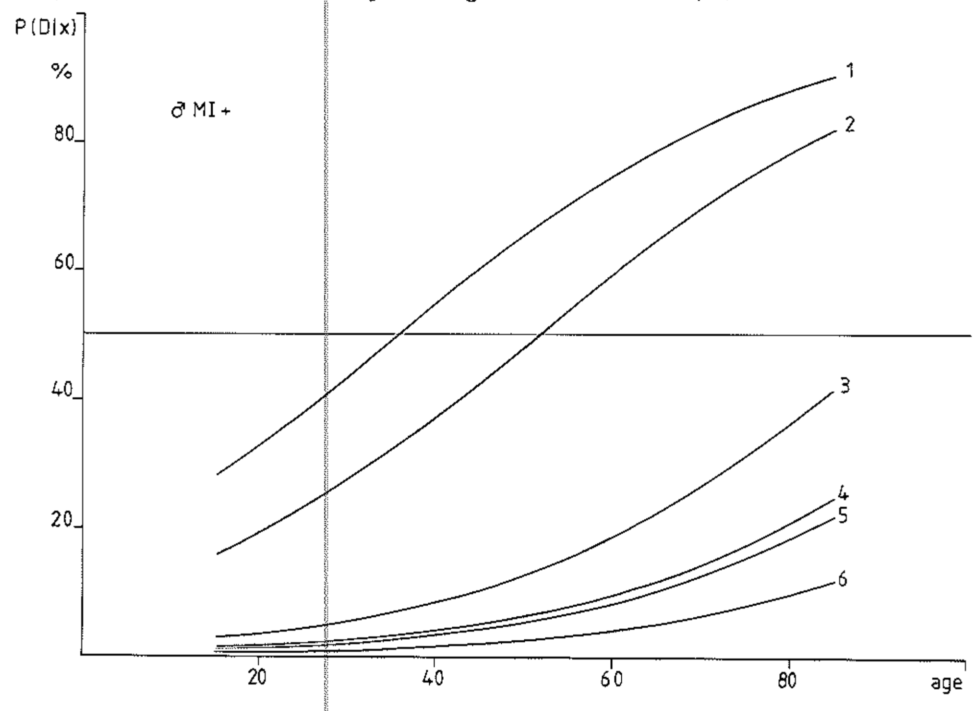
ECG-finding did not occur among controls in this group. Coefficients of one variable were always of the same sign in the two groups. With a few exceptions, coefficients for patients with MI were lower than those estimated in the entire data set, while coefficients for patients without MI were generally higher. Also, many Z-values (see 3.4) were not significant in patients with MI while in patients without MI this was rarely the case. Both these findings suggest that the predictive value of these variables is greater for patients without MI than for patients with MI.

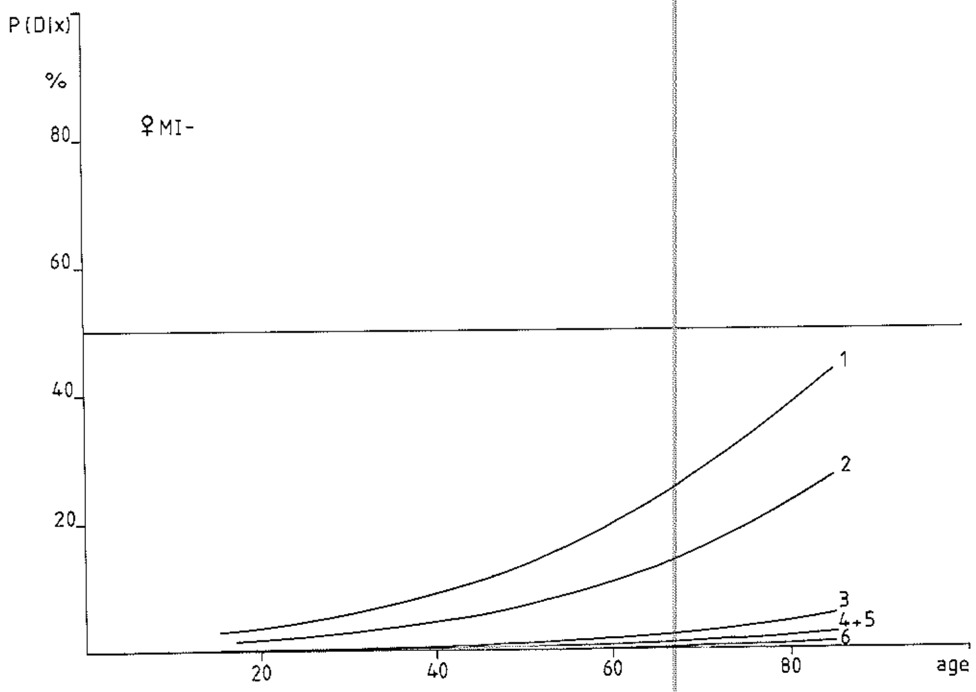
4.5 Predicting cardiac death by means of the multivariate model

The probability of cardiac death within 18 months after ECG-recording given a particular combination of characteristics, $P(D|X)$, was computed

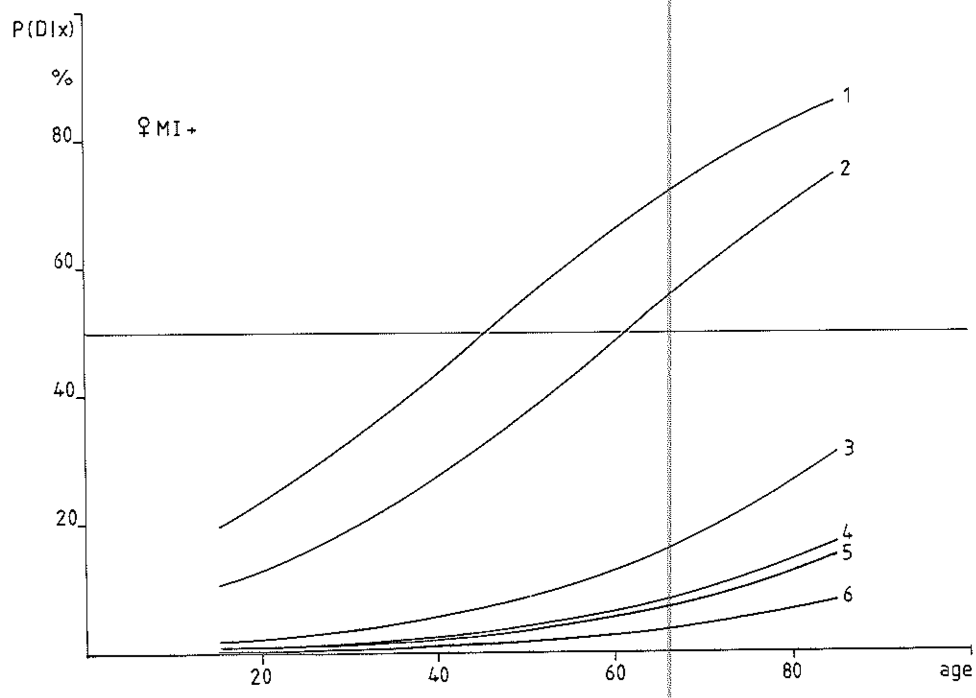


Figures 4.5/1-4
P(D|X) by age for several categories of patients.
Computations based on the equation given in table 4.4/4.





Numbers in the figures refer to particular combinations of characteristics.
For explanation see page 82.



by means of the multivariate equation given in table 4.4/4. The formulas used for these computations have been given in section 3.5.1.
For males and females with and without MI $P(D|X)$ was plotted against age for six categories of patients (figure 4.5/1-4). These categories were characterised by the presence of:

1: none of the characteristics included in the equation
2: non-sporadic doublets and/or ventricular tachycardia
3: use of digitalis
4: intermittent IVCD
5: both continuous atrial fibrillation and use of digitalis
6: non-sporadic doublets and/or ventricular tachycardia, continuous atrial fibrillation and use of digitalis.

These graphs give a visual representation of the information contained in the coefficients in table 4.4/4. They show clearly that risks were on a higher level for patients who sustained an MI prior to ECG-recording. Similarly, $P(D|X)$ was lower for women than for men with otherwise comparable clinical characteristics. $P(D|X)$ was the same for patients who used digitalis or patients who had non-sporadic doublets and/or

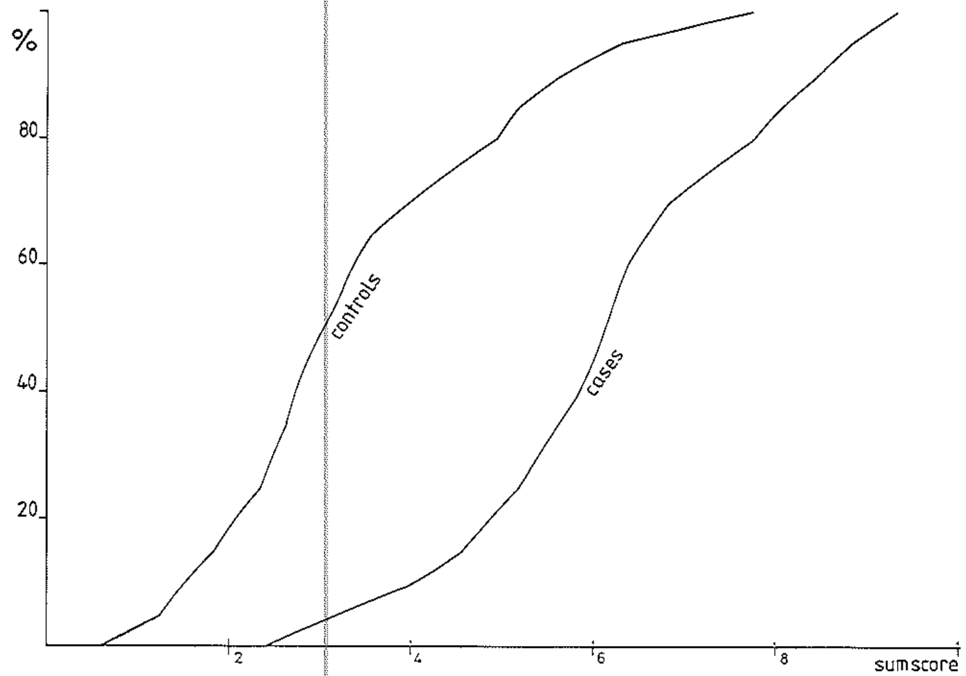


Figure 4.5/5
Distributions of the sum-score for cardiac cases (n=123) and controls (n=433) based on equation 4 (table 4.4/4) for the prediction of cardiac death.

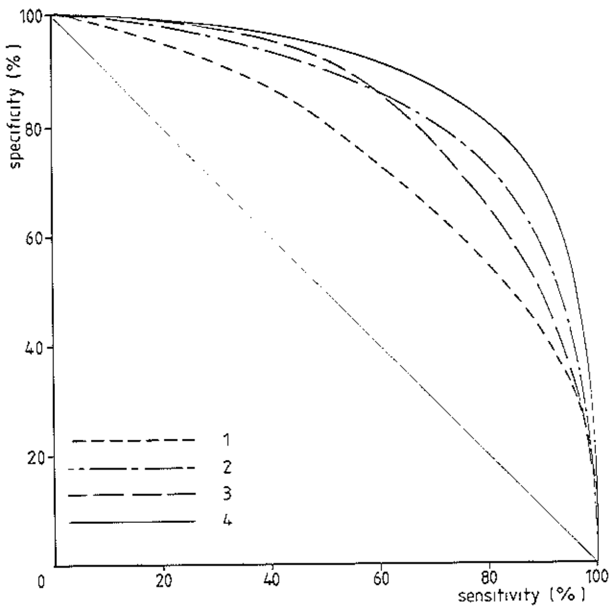


Figure 4.5/6
ROC curves representing the performance of the equations for the prediction of cardiac death given in tables 4.4/1-4

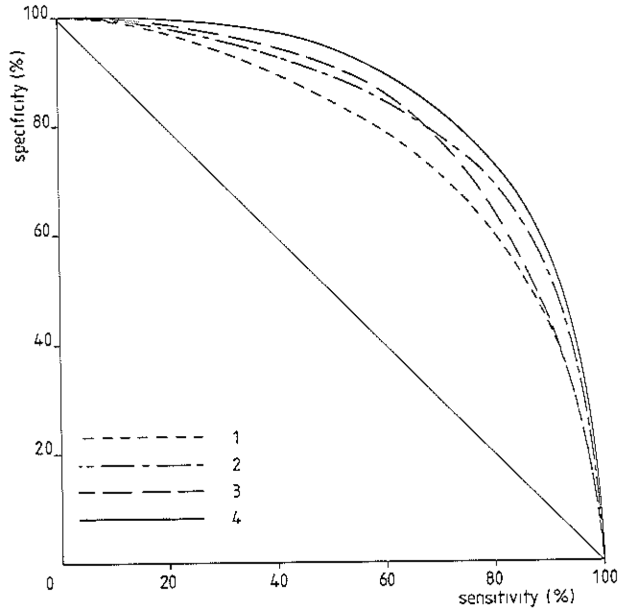


Figure 4.5/7
ROC curves representing the performance of the equations for the prediction of overall mortality given in tables 4.4/1-4

ventricular tachycardia. The presence of continuous atrial fibrillation (accompanied by the use of digitalis) greatly increased the risk of cardiac death. The magnitude of this increase was greater when MI was present.

The sum-score was computed for each patient. As an example, the cumulative distributions of the sum-score for cardiac cases and controls are shown in figure 4.5/5. In this particular figure, the sum-score was computed using equation 4 for the prediction of cardiac death. From this figure, sensitivity can be estimated as the proportion of cases with a sum-score greater than a chosen cut-off value and specificity as the proportion of controls with a sum-score smaller than or equal to that chosen value. Repeating this procedure for several cut-off values of $P(D|X)$ permitted the Receiver Operating Characteristic (ROC) curve to be plotted. In figure 4.5/6 the four ROC curves are shown which are based on the four multivariate equations constructed for the prediction of cardiac death given in tables 4.4/1-4. The four ROC curves based on the four equations constructed for the prediction of overall mortality (given in the same tables) are shown in figure 4.5/7.

The ROC curves provide a visual representation of the performance of an equation (see 3.5.2). One possible use is to choose a particular trade-off between sensitivity and specificity and use the corresponding cut-off point for prediction.

As an example, choosing a sensitivity of 90%, specificity is 41% when only age and sex are used for the prediction of cardiac death (figure 4.5/6). Specificity rises to 50% when ECG-findings are also taken into account but to 59% when clinical variables are added to age and sex. When prediction is based on both clinical information and ECG-findings, specificity is 72% at 90% sensitivity. Comparing figures 4.5/6 and 4.5/7 it can be seen that the four curves which are concerned with the prediction of overall mortality lie more closely together than do the four curves which are concerned with the prediction of cardiac death. In the terms of the previous example, this means that, for a chosen sensitivity, the increase in specificity going from one curve to another is smaller when predicting overall mortality. In fact in figure 4.5/7 for equations 1, 3, 2 and 4 specificity is 42%, 42%, 57% and 61% respectively at 90% sensitivity.

5 DISCUSSION I: METHODS

5.1 Study design

A sample of 5095 patients was successfully followed up for at least 18 months after the recording of a 24-hour ECG. Complete baseline information was collected for two subsamples of 433 controls and 195 cases. The controls were a 9% random sample from the 4882 patients who survived 18 months and the cases were the 213 patients who died within 18 months excluding those for whom information was missing (see figure 4.3/1).
The scale of the problem was greatly reduced by restricting the statistical analysis to cases and controls only. This had obvious advantages compared to an analysis based on complete baseline information collected for all patients in the sample.
Yet the same parameters can be estimated with both methods. It has been shown in section 2.4 that there is no fundamental difference between the two estimators of the odds ratio which measures the association between a baseline variable and mortality in the population from which the sample is assumed to be drawn. Because the sampling fraction of the controls is known, the absolute risk of death for patients with a particular characteristic can also be estimated. The same sensitivity and specificity of prediction can be estimated with both methods. The prevalence of patient charateristics in the sample can be estimated from the prevalence among cases and controls.
One can raise the question whether the reduction of the number of controls from 4882 to 433 causes a serious loss of statistical power. In section 2.4 it was argued that, given the number of cases, the statistical power depends on k - the ratio of the number of controls to the number of cases.
If all patients in the sample had been involved in the analysis k would have been equal to 22.9. In the present study, k equals 433/195=2.2 but 433/123=3.5 when only cardiac deaths are considered.
Oliphant & McHugh (1981) give formulas for the computation of the minimal relative risk that can be detected by means of a univariate statistical test given the numbers of cases and controls, the significance level of the test, the statistical power of the test and the proportion

Table 5.1/1

Minimal relative risk that can be detected by a univariate two-sided statistical test based on 123 cases and a variable number of controls (n). P is the proportion of exposed controls.

P	RR n=123	RR n=433	RR n=4882	RR n=123	RR n=433	RR n=4882
.1	.08	.19	.25	3.08	2.51	2.28
.3	.36	.45	.49	2.36	1.98	1.87
.5	.43	.51	.55	2.38	1.97	1.87
.7	.43	.51	.55	2.84	2.30	2.05
.9	.33	.40	.45	13.22	5.32	3.98

$2\alpha=.05$, $\beta=.10$

of exposed controls (i.e. controls having the characteristic under consideration). Using these formulas the minimal detectable relative risk (which in the present study is approximated by the odds ratios) was computed for the situation that the number of cases equals 123 and that 1) the number of controls equals the number of cases (k=1), 2) the number of controls equals 433 (k=3.5), 3) the number of controls equals 4882 (k=22.9). Table 6.1/1 gives the results for different proportions of exposed controls. From the table it is evident that the smallest detectable relative risk is closer to unity when the number of controls is larger. However, the 'gain' is much greater when this number is increased from 123 to 433 than when the increase is from 433 to 4882. The 'gain' of analyzing the data of all survivors rather than the data of a random sample is clearly outweighed by the extra cost involved in such an analysis.

Controls were randomly selected from all non-cases in the sample. The sampling procedure (see 2.6) ensured that the number of controls from one hospital was proportional to the number of non-cases in the sample from that hospital and that the dates of ECG-recording of controls were evenly distributed over the two and a half years of the study period. There were a number of advantages to the random sampling of controls as compared to the possibility of matching controls to cases.
Firstly, randomly sampled controls are representative of the non-cases in the sample. This fact permitted the estimation of the prevalence of

arrhythmias and other characteristics in the sample from the prevalence among cases and controls (see 3.1).

Secondly, in a matched analysis the matching variables do not appear in the multivariate equation. If age were one of the matching variables, the increasing mortality with age would need to be accounted for by inserting age-specific prior probabilities into the corrections of the constant in the equation (see 3.5.1). If in the present study we had matched for age, sex and indication, this would have necessitated the estimation of the prior probability in 144 different categories of patients (8*2*9, assuming eight 10-year age-intervals and 10 mutually exclusive categories of indication). This would have been possible with the data available to us. However, some of these estimates would have had to be based on small numbers of patients. Furthermore, it would have made the correct use of the prognostic equations considerably more complicated as the correct constant would have had to be selected for each patient.

Thirdly, because of the difficulties involved in finding matched controls, the number of controls per case would have been limited to only two. The ratio k would thus have equalled 2 compared to 3.5 in the present study and this would have meant a non-negligible loss of statistical power. This point is emphasized by Kupper et al (1981) who concluded on the basis of theoretical work that if matching reduces the size of the control group, there may be a meaningful gain in statistical efficiency from random sampling over matching.

Fourthly, the estimation of coefficients for the multiple logistic regression equation by means of maximum likelihood is considerably more complicated for matched data and is therefore extremely costly in terms of computer time.

5.2 Quality of the available data

The majority of the baseline data were retrieved from the archives of Cardiolab (see 2.5,7) and had been collected in the context of usual medical care. This places certain limitations on the quality of these data.

One limitation is that physicians did not always provide accurate information on the request form. This occasionally caused difficulties in the identification of a patient but these were normally overcome.

However, inaccuracies in the indication for ECG-recording and the medication used at the time could not afterwards be detected. Thus use of medication may have been under-reported and the 46% of patients without medication (table 4.1/2) may be too high an estimate.
Indications are similarly subject to error (see 6.2). When the prognostic significance of certain indications or use of certain medications is considered, under-reporting does not lead to spurious associations. As one compares the prognosis of a group of patients with a particular indication or medication with the prognosis of a group which comprises patients without and with that characteristic (due to the under-reporting), the association of the characteristic with mortality (if present) will only be weakened by under-reporting, unless under-reporting occurred more frequently in patients with a good prognosis.
One may hypothesize that this is the case, because a physician might pay more attention to request forms of patients with a more serious condition. This would not have influenced the finding that palpitations indicate a good prognosis. It may have influenced the finding that use of digitalis and of diuretics are of prognostic significance. However, prognostic significance of the use of these medications has also been reported by investigators who did collect their data in the context of a specific follow-up study (Ruberman, 1977, 1980).

The same line of argument may be followed with regard to the analysis of the 24-hour ECG. The occurrence of arrhythmias may have been under-reported due to inattention of the analysts. The analyst may selectively give attention to those parts of the tape which correspond in time with particular activities or symptoms noted in the patient's diary. Again, the analyst may be looking for a particular kind of arrhythmia because of details given on the request form and therefore be less attentive to other arrhythmias. If the analyst is aware that the condition of the patient is serious, this may result in increased attention during the analysis.
It is difficult to specify the precise effect of these mechanisms on the present results. However, it seems unlikely that the continuous presence of atrial fibrillation or first degree AV-block would not be detected and under-reporting may be presumed to be absent for these arrhythmias. Similarly, arrhythmias which occur frequently are less likely to be missed than arrhythmias which occur only sporadically. Thus intermittent

IVCD and escapes are more likely to be under-reported than are the arrhythmias which have been termed non-sporadic in table 4.3/5. Even if under-reporting occurred to a significant degree, it remains a matter of speculation whether this occurred in such a way that artifacts were obtained.

5.2.1 classification of arrhythmias

Another limitation of the present data lies in the criteria which have been used for the classification of arrhythmias. These criteria were designed to suit the needs of Cardiolab as a diagnostic service rather than the views of the present investigator. This is particularly evident where it concerns the frequency with which arrhythmias occurred. While the investigator would prefer, for example, counts of the number of PVCs in (a part of) the tape, the need for efficiency does not allow such time-consuming procedures. The 5-point scale (see 2.2.4) yields only semi-quantitative information and is subject to personal judgement. The definition of the categories on the scale in terms of percentages of recording time is obviously not rigid. Inaccurate information as to frequency leads to underestimation of the association between frequency and mortality.

Another difficulty is that criteria may change over time. This was the case with the criteria for early cycle PVCs, also referred to as the R-on-T phenomenon. In the course of time it was found that electronic filtering could induce the appearance of early cycle PVCs on the oscilloscope of the analysis unit. The criteria were then adapted to prevent the detection of a great number of false positives. As it was difficult to trace afterwards exactly which definition had been used for a particular tape, it was decided not to consider early cycle PVCs in the present study.

Similarly, a patient could be reported as having both uniform and multiform PVCs meaning that during a certain part of the recording time uniform PVCs occurred while during another part of the recording time multiform PVCs were detected. Sinus tachycardia had been defined as a heart rate exceeding 150/min. The more common threshold of 100/min. was not used since during daily activity a heart rate of 100/min. was reached by many patients, resulting in an exaggerated number of patients reported as having sinus tachycardia.

Table 5.3/1

Observed and estimated prevalence (%) of indications

indication	observed	estimated	se
myocardial infarction	14	14	1.5
coronary heart disease	7	7	1.1
palpitations	38	44	2.2
dizziness	14	13	1.5
syncope	18	17	1.7
evaluation of therapy	4	4	.9
evaluation of arrhythmia	28	27	1.9
evaluation of pacemaker	1	1	.4*
other	3	6	1.0

se = standard error of estimate

* normal approximation not appropriate see 3.1.1

5.3 Estimation of prevalence in the sample

In chapter 4.1 estimated frequency of occurrence in the sample has been given for characteristics which were known for patients in the subsamples of cases and controls only. The proportion p_s of patients in the sample with a particular characteristic was estimated as a weighted average of the proportions of cases and controls with that characteristic. The standard error of $\hat{p}_s$ was estimated as a weighted sum of the standard errors in the two strata of cases and controls. The latter permitted the construction of a confidence interval for the true proportion p_h of all cases or all controls with a particular characteristic.
To demonstrate the reliability of this estimation procedure, the observed prevalences of the indications (which were known for all patients in the sample, see 2.5) were compared to those estimated on the basis of the indications of cases and controls (table 5.3/1). There is good agreement between the two, except for the categories 'palpitations' and 'other'. In these categories the observed value p_s lies outside the estimated 95% confidence interval. The indications for cases and controls were coded more scrupulously than were the indications for all patients in the sample. This may be the reason for the higher frequency of the indication 'other' in cases and controls. For the estimated proportion of patients

with the indication 'evaluation of pacemaker', the normal approximation could not be used to construct a confidence interval because $n_h\hat{p}_h<10$ in the subsamples of both cases and controls.

As the subsample of cases on which these estimates were based included virtually all cases, the finite population correction (fpc) was used to correct the standard error per stratum $S(\hat{p}_h)$ (see 3.1.1).
However, the fpc $(1-n_h/N_h)$ could not be determined for cases with a cardiac cause of death. Though $n_{1'}$ - the size of the subsample of cardiac cases is known (and equal to 123), $N_{1'}$ - the total number of cardiac cases in the sample, is not known since cause of death is unknown for the 18 cases for whom no baseline information was available. For this reason, $S(\hat{p}_{1'})$ has not been given for cardiac cases in tables 4.3/1-3 and 4.3/5. Similarly, when univariate distributions are given separately for patients with MI and patients without MI (tables 4.3/2,3,6,7), presence or absence of MI is unknown for cases and controls not included in the subsamples, so that the total number of cases (controls) with (without) MI in the sample are again unknown.

Use of the fpc caused the standard errors to become smaller and the corresponding confidence intervals to become narrower. For controls, this correction was only small ($\sqrt{1-\phi_2}$=.95, see 3.1.1) as this subsample comprised only 9% of the survivors in the sample. For cases it was considerable ($\sqrt{1-\phi_1}$=.29).

It might be argued that use of the fpc would have been unnecessary if the subsample of cases had been considered as randomly drawn from an infinite population of cases (i.e. all patients dying within 18 months of a first 24-hour ECG, possibly through a cardiac cause). This point of view was adopted in section 2.4 in order to show that the same odds ratio can be estimated from the sample as a whole and from the subsamples of cases and controls. Indeed, when studying associations of arrhythmias and mortality, one is interested in relationships which are not dependent on the actual data but represent a biological reality and will therefore continue to exist in other points in time (the future) and place (other parts of the world). When studying the prevalence of arrhythmias, however, one is less interested in establishing the prevalence of arrhythmias for all patients undergoing 24-hour ECG-recording at any time or place, than in describing the clinical characteristics of the actual sample being studied.

Use of a normal approximation to the binomial distribution for the construction of confidence intervals for $\hat{p}_h$ gave no difficulties (that is, $n_h\hat{p}_h$ was not less than 10) except when $\hat{p}_h$ was very small i.e. less than 6% for cases (n_1=195) or less than 3% for controls (n_2=433). However, when estimating the prevalence of arrhythmias in the sample for categories of age and sex (tables 4.1/6,7) or of indication (tables 4.1/8-10), the numbers of cases and controls on which these estimates were based were reduced (table 4.1/5). This often caused the use of the normal approximation to become invalid. Therefore, standard errors were either not given in these instances or were marked with an asterisk.

An alternative might have been to base these estimates on 'exact' confidence intervals for $\hat{p}_h$ as described by Stern (1954). Tables (Diem & Lentner, 1968) for such confidence intervals are based on the assumption of an infinite population.
Theoretical derivations for the 'exact' confidence interval of a difference of two proportions have been given by Santner & Snell (1980). An 'exact' confidence interval of other linear combinations of two proportions, such as a weighted average, might conceivably be derived from the same theory. Such derivations were beyond the scope of the present study, however. Also, computer programs for these procedures are not readily available and would be rather costly in terms of computing time.
For these reasons, it was decided to use the normal approximation and accept a reasonable degree of imperfection.

5.4 Tukey's median polish

The 'median polish' method was used to explore relationships between indication and age. This technique applies concepts from classical analysis of variance with this difference that the median rather than the mean is used as the principal measure of centrality. As a consequence, an iterative procedure is necessary to compute the matrix of estimated expected values (E) and the matrix of residuals (R). This procedure is amply described elsewhere (Tukey, 1977; Velleman & Hoaglin, 1981).

Because the median is less sensitive to the presence of extreme observations than the mean, row and column effects estimated by the 'median polish' technique are more stable than are those based on means. The same argument, which has been set out in more detail elsewhere (Velema, 1982), applies to the frequently used method of estimating expected frequencies based on the marginal totals. Deviations from the postulated model will therefore be more pronounced when the median polish technique is used. Since interest was focused on these deviations in the present analysis, the 'median polish' was preferred to the alternatives mentioned.

5.5 Assumptions in the Kaplan-Meier method

In the Kaplan-Meier method of estimating the probability of survival (see 3.2) the assumption is made that censoring is independent of the mechanisms which cause the endpoint to be reached. In other words, the reasons why patients are lost to follow-up should have no relationship to the prognosis of the patient. Clearly, mortality will be overestimated if patients with a good prognosis are no longer followed. Similarly, mortality will be underestimated if patients who approach death are more often lost to follow-up than are other patients.
In the present study every possible effort was made to ensure that follow-up would be complete. Only 35 patients (0.7%) could not be followed for at least a full 18 months after ECG-recording. The reason for incomplete follow-up was usually that the patient moved to another country. This concerned both people of Dutch nationality who went abroad and people of other nationalities who returned to their home country. Although the Dutch migrants were presumably all healthy, it is unlikely, given the small proportion of censored data, that this bias will have influenced the results to a significant degree.
However, when 18 month follow-up was complete no particular effort was made to follow the patient any longer. Information was collected in the new place of residence when a patient had moved within 18 months ECG-recording but not when the patient had moved more than 18 months after. However, from our experience with moves within 18 months, we have the impression that elderly patients who moved to another place of residence had a greater probability of death. For instance, patients who moved to old-peoples homes or other institutions, who left the city, or who returned to their place of birth. If this impression is correct, mortality

after 18 months in figure 4.2/1 may be slightly underestimated. Fifteen percent of patients were 70 years or older, but the proportion of patients who had moved was not recorded.

5.6 Classification of causes of death

Two sources of information regarding the cause of death of cases were available to us. Firstly, cause of death was included in the questionnaire (see 2.7) which was sent to the referring physician or to the general practitioner. Secondly, information was obtained from the physician who was attending the patient at the time of death. This may or may not have been the same physician who answered the questionnaire. Cause of death was obtained from the attending physician for 180 cases and through the questionnaire for 103 cases. Information from at least one source was available for all 195 cases. For 88 cases, cause of death was known from both sources.

Age and sex of each case as well as the indication for ECG-recording were available from the Cardiolab archives (see 2.5).

On the basis of this information, deaths were classified as cardiac, cardiovascular or non-cardiac as follows.

First, the 26 cases with any kind of neoplasm were classified as non-cardiac.

Then, 83 cases for whom a myocardial infarction was mentioned in at least one source were classified as cardiac. In 21 cases the death had been described on the questionnaire as 'sudden'. An MI was mentioned for 13 of these 21 patients and these had already been classified as cardiac for that reason. The other 8 'sudden' deaths were also classified as cardiac. If no other information was available than that the patient had CHD the death was assumed to be cardiac (15 cases). Eleven deaths from congestive heart failure and 2 from cardiomyopathy were classified as cardiac. One death which was due to cardiac standstill, two due to valvular heart disease and one described by the general practitioner as cardiac, were all classified as cardiac thus making full the total number of 123 cardiac deaths.

Eleven deaths due to cerebrovascular events were classified as cardiovascular. However, four cases for whom a cerebrovascular event was mentioned in addition to a myocardial infarction, had already been

Table 5.6/1
Classification of cases according to cause of death and the source(s) from which information regarding cause of death was available.

	questionnaire	attending physician	both
	%	%	%
cardiac	53	60	68
non-cardiac	27	18	20
cardiovascular	20	22	12
total number(=100%)	15	92	88

classified as cardiac. Other deaths classified as cardiovascular (24) included deaths due to arterial thrombosis, due to complications during or after surgery for cardiovascular problems and deaths of which the causes given were partly of a cardiac, partly of a non-cardiac nature. If there was no evidence for a cause of death related to cardiovascular disease the patient was classified as non-cardiac (e.g. renal problems, pneumonia; 11 patients).

Cases were categorized according to cause of death and according to the source(s) from which the information regarding cause of death came (table 5.6/1). From this table it appears that a decision as to a definite cardiac or non-cardiac cause of death could more often be made if information was available from both the questionnaire and the attending physician.

The physician who filled in the questionnaire was more likely to list the cause which actually precipitated death, if known to him or her. The attending physician, on the other hand, tended to give information about the underlying disease without specifying whether or how this was related to the occurrence of death. This explains why, as mentioned above, for 15 cases no other information was available than that the patient suffered from CHD.

It is inevitable that a degree of arbitrariness will be present in any classification of causes of death. The classification procedure given above only illustrates that it is impossible to determine with 100% certainty whether or not a patient died of a cardiac cause and that sometimes a case classified as cardiac may in reality have died from a non-cardiac cause. Even so, odds ratios usually increased when the analysis was restricted to cardiac deaths only (sections 4.3, 4.4) as may be expected if the variables considered are assumed to be specifically associated with cardiac death. This suggests that the present classification, though not perfect, is reasonably reliable. The fact that 37% of cases did not die of a cardiac cause (figure 4.3/2) points once more to the diversity of disorders which was present in patients in the sample.

5.7 Selection of variables

The computer program which was actually used for the initial screening of variables (see 3.4.1) was the procedure 'Regression' in the interactive statistical program package SCSS (Nie et al, 1980). When the dependent variable is dichotomous, the coefficients in a multiple linear regression equation differ only by a constant from the coefficients in a linear discriminant equation (Kleinbaum & Kupper, 1978). The constant depends on the numbers of cases and controls and on the coefficient of determination R-squared which is unique to the particular regression equation considered. The ratio of a coefficient to its standard error is identical in both instances. SCSS permitted one by one inclusion/exclusion of variables in the equation as well as forward selection, backward elimination or a stepwise procedure.
The usual procedure was to add each eligible variable to equation 1 or equation 2 and test for significance. Subsequently, a model was constructed of variables which had been found to contribute significantly to prediction, independent of age and sex (equation 1) or of relevant clinical variables (equation 2). Interaction variables were also considered in this process. The interactive computer program made it possible to compute interaction variables 'while you wait' and to see on the terminal the effect of including a variable on the coefficients and test-statistics of variables already in the equation.
Patterns of collinearity (i.e. the effects of associations between variables on the size of the coefficients) were easily recognized in this way and possible alternatives could be summarized efficiently.
When a choice had to be made between correlated variables, prior views as to the relative importance of variables and ease of interpretation were also considered. In other words, information 'not embodied in the

numbers presented to the computer' was taken into account. Such an approach is greatly facilitated by the availability of interactive computer programs. In our opinion, some automated procedure for variable selection can never replace the personal judgment of the investigator. Henderson & Velleman (1981) rightly state, that to tolerate 'objective' decisions from a computer is a subjective decision to abdicate responsibility.

The ratio of a coefficient to its standard error (the Z-statistic) was used to test whether the coefficient was significantly different from zero. It follows from the central limit theorem that for increasing numbers this statistic approaches the standard normal distribution. Since the coefficients in the multiple logistic regression equation were estimated through the maximum likelihood method (see 3.4), the likelihood ratio might have been used to test their significance (Breslow & Day, 1980). The likelihood ratio test was in fact used in a number of instances and there was never disagreement between the outcomes of this test and of the test based on the Z-statistic. This is in accordance with the statement by Breslow & Day (1980) that in large samples these statistics give approximately equal numerical results under the null hypothesis and have the same distribution.
Another criterion for the selection of variables which has been suggested is the error-rate of misclassification. Habbema and Hermans (1977) have given examples where use of the Z-statistic and of the error-rate lead to different results. However, these examples concerned discrimination between three groups and the authors imply that for two group-discrimination the two approaches lead to similar results.

5.8 Estimation of sensitivity and specificity

ROC curves were used to evaluate the performance of the logistic equations given in section 4.4. Using a number of different cut-off values for the sum-score of each equation, predictions were made for cases and controls and the predicted outcome of each patient was compared to the observed outcome (see 3.5.2). Thus the same subsamples of patients were used to estimate the coefficents of an equation and to evaluate the performance of that equation.

Lachenbruch & Mickey (1968) have shown that, if the sample used to estimate the coefficents of the prognostic equation is not large, this method (which they call the resubstitution method) gives too optimistic an estimate of the sensitivity and specificity associated with that equation. A better estimate would be obtained if the sample used for evaluation were independent of the sample used for estimation of the coefficients. This estimate would be unbiased and it would follow a binomial distribution.

One way to achieve this would be to use the equations which resulted from the present study to predict mortality in a second cohort of patients which in turn could be followed up. From the predicted and observed outcomes in this second cohort sensitivity and specificity might be estimated and confidence intervals for these estimates could be based on the binomial distribution. Furthermore, this approach has a great practical appeal as it gives a direct answer to the question how well a particular equation will predict mortality in future patients of whom it is unknown a priori whether they will survive or die. However, few researchers can afford the time and the money to follow up a second cohort of patients. In the area we are dealing with here, Moss et al (1976) and Luria et al (1979) have used this approach.

A less costly variant of this method would be to split the dataset of cases and controls into two subsets and use one subset for learning (i.e. estimation of coefficients) and the other subset for testing (i.e. evaluation of performance). The estimates of sensitivity and specificity resulting from this evaluation might be treated as if applying to the equations based on the entire dataset of cases and controls. This would give an impression of the performance of these equations assuming that this performance is not worse than the performance of the corresponding equation based on a part of that dataset.

Table 5.8/1
Sizes of the subsets resulting from a division of the cardiac cases and controls.

	subset 1	subset 2
cases	63	60
controls	214	219

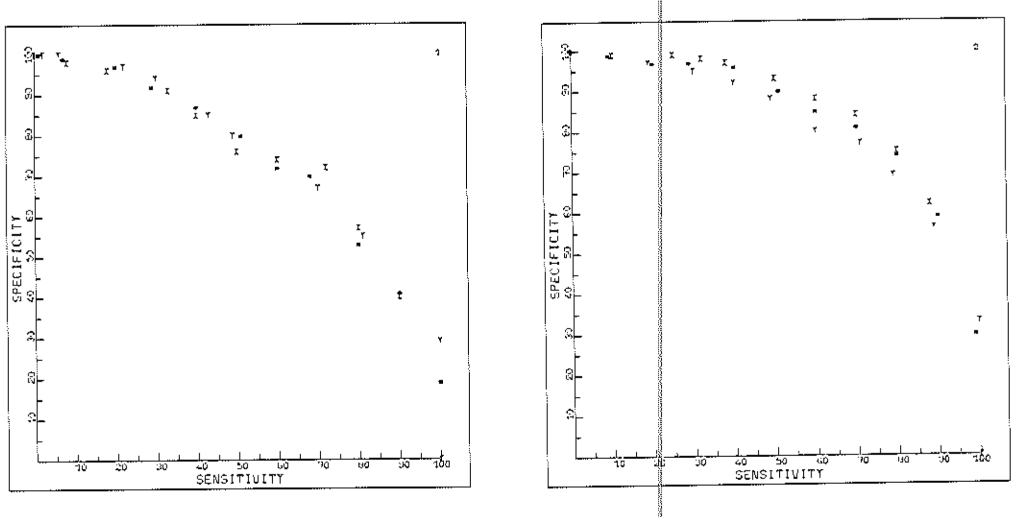
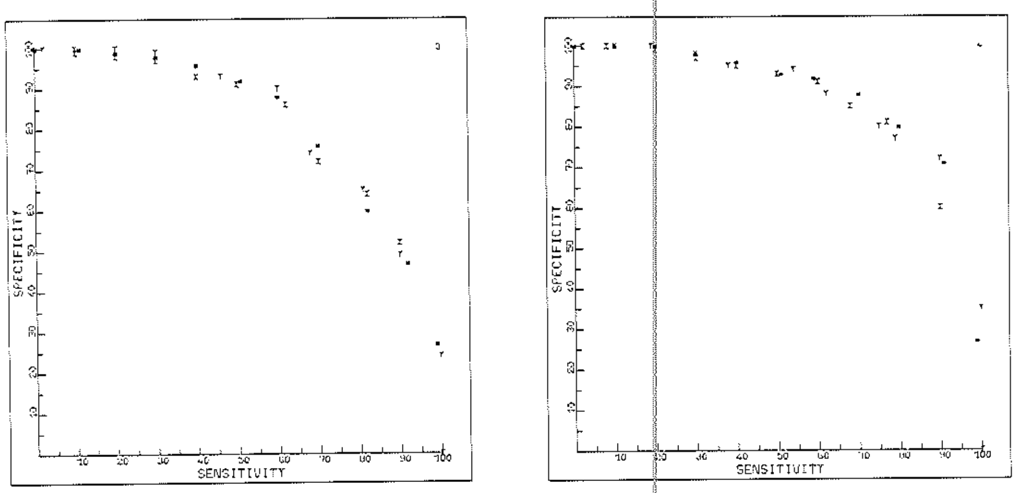


Figure 5.8/1
Points of ROC curves representing the performance of prognostic equations based on subset 1, which have been evaluated in subset 1 (X) and subset 2 (Y). A third set of points (*) indicates the curve already given in figure 4.5/6.
Numbers in the (100%,100%) point correspond to those given in section 3.4.1



An often used application of this idea is the jack-knife method by means of which a prediction would be made for each patient using an equation based on the entire dataset with the exclusion of that particular patient.
In order to see whether the estimates of sensitivity and specificity reported in section 4.5, which were obtained by means of the resubstition method, were misleading, the following was done.

The dataset of cases and controls was split into two subsets of approximately equal size (table 5.8/1).This was done by numbering the patients sequentially and assigning patients with an even number to one subset and patients with an uneven number to the other subset. Only cases with a cardiac cause of death were considered. Subset 1 was used to estimate coefficients for four logistic equations comprising the same variables as the equations given in tables 4.4/1-4 for the prediction of cardiac mortality. The sum-scores of these equations were used to predict cardiac mortality both in subset 1 (resubstitution) and in subset 2 (independent sample) for a number of cut-off values (see 3.5.2). Sensitivity and specificity were estimated for each of these predictions.

The results for each equation are shown in a graph (figure 5.8/1) together with the estimates of sensitivity and specificity associated with the corresponding equation as reported in chapter 4 (figure 4.5/6). From figure 5.8/1 it is apparent that the three different estimates lie closely together in all instances. The estimates from subset 1 were not consistently more optimistic than the estimates from subset 2. Nor were the estimates based on the entire dataset more optimistic than those based on the subsets. If we were to construct confidence intervals for the estimates based on subset 2, the other two estimates would lie within its range in virtually all instances. Evidently, the subsamples of cases and controls were sufficiently large to avoid the bias associated with the resubstitution method against which Lachenbruch & Mickey warned.

6 DISCUSSION II: CHARACTERISTICS OF THE SAMPLE

Patients in the sample were under treatment in 40 different hospitals. Fifty eight percent of patients were under treatment in hospitals located in Zuid-Holland, the province which includes Rotterdam (figure 4.1/1). From the map it can be seen that during the study period Cardiolab's catchment area steadily widened as the turnover of 24-hour ECGs grew.

6.1 Patient selection

Besides difference in geographical location, patients in the sample also differed with regard to their state of health. Ambulatory 24-hour ECG-recording is a useful diagnostic aid in a variety of conditions and each cardiologist or internist had his or her own policy with regard to its application. This policy was dependent on such things as the kind of hospital in which the physician practised, the kind of patient population he or she cared for and the familiarity with this kind of investigation. Thus, one physician might make a liberal use of the Cardiolab service for many different kinds of patients, while another might restrict its use to one or two well-defined categories of patients.

Patients were thus not selected for the recording of a 24-hour ECG on the basis of uniform well-defined criteria. Consequently, the sample includes patients with a variety of cardiac disorders. For example, patients with idiopathic hypertrophic subaortic stenosis (IHSS) may present with palpitations or syncope (Ingham et al, 1975) and have undergone 24-hour ECG-recording for this reason. Alternatively, the diagnosis may have been known and have in itself been a reason for the recording of a 24-hour ECG. It is not known whether or not the risk associated with the presence of ventricular arrhythmias in patients with IHSS is different from that in patients with other conditions. *If* it is, the results reported here will depend on the proportion of patients with IHSS in the sample. This dependence can be removed by including a variable in the prognostic equation which indicates presence or absence of IHSS. However, patients with IHSS have not been identified. The same applies to patients with other disorders, some very serious, some benign. It should even be recognized that a certain proportion of patients in the sample may have been perfectly healthy. The exact distribution of these various conditions in the sample may have influenced the results of this study. However, this distribution is not known.

What is known of all patients in the sample is that they had attended the out-patient clinic and had presented with signs and/or symptoms of such a nature that the physician decided that a 24-hour ECG should be recorded. Consequently, the present results can only be extrapolated to a patient population which can be subjectively defined as those who, through their interaction with the physician, give rise to the recording of a 24-hour ECG.
It must be recognised, however, that this definition is dependent on the policy of the individual physician with regard to the use of 24-hour ECG-recording. A change in this policy will ultimately change the patient population thus defined and extrapolation of the present results may be no longer valid.
For example, the publications reporting the prognostic significance of ventricular arrhythmias in post-MI patients (table 7.2/1) have stimulated physicians to record 24-hour ECGs for the evaluation of the prognosis of the post-MI patient. Consequently, many such patients have undergone 24-hour ECG-recording in recent years, who would not have been selected for this investigation during the period with which this study is concerned. Given the different prognostic significance of ventricular arrhythmias for post-MI patients in the present sample and for those studied elsewhere (see 7.2), it is reasonable to suppose that the present results for post-MI patients would not be reproduced if a sample from a more recent period were considered.
Similarly, the present results might not be applicable in the future if this thesis stimulated physicians to record 24-hour ECGs for the sake of evaluating the prognosis of the patient rather than for any of the indications used up to the present period.

The report of the ECG-analysis was sent to the referring physician (see 2.2.4) and subsequently utilized as one of the bits of information which enabled him or her to select the treatment strategy for that individual patient. This implies that the prognostic information derived from this study must be interpreted as 'what happens to a group of patients with a particular arrhythmia when they are treated to the best of our present knowledge'. In other words, the conclusions are conditional on treatment practices current at the time of the study. Naturally, this is also true for other similar studies (Ruberman, 1980; Moss, 1977).

6.2 Indications

In the absence of specific diagnostic information, the indication for ECG-recording as given by the physician on the request form might help to distinguish different categories of patients. Two indications refer to a particular diagnosis (myocardial infarction, coronary heart disease), three to the presence of symptoms (palpitations, dizziness, syncope) and two to therapy (evaluation of therapy, evalution of pacemaker). All indications pertain to the detection of arrhythmias and not to the detection of ST-segment deviations as the latter could not be reliably detected with the available instruments. However, it is uncertain, if not unlikely, that each physician meant the same thing when ascribing a patient to a particular category of indication. As indications were not well-defined a priori it may be useful to study a posteriori the characteristics of patients with different indications. This may provide clues as to the criteria that were actually used for the choice of a particular indication.

6.2.1 myocardial infarction

From tables 4.3/1 and 4.3/3 it can be estimated that for approximately 46 (6%) of all the 668 patients with the indication MI this indication could not be traced back to an acute event which was documented in the medical records and occurred at a particular date. Conversely, an estimated 415 patients (9%) of all patients without the indication MI actually did sustain an MI at some time prior to the 24-hour ECG.
Of course, a previous MI may not be the actual reason for the recording of a 24-hour ECG and may therefore not appear on the request form. Even so, we should be aware that indications are subject to error even for such a relatively well-defined condition as an MI.
Very few physicians used 24-hour ECG-recording as a routine pre-discharge procedure. During the study period, the prognostic value of such a

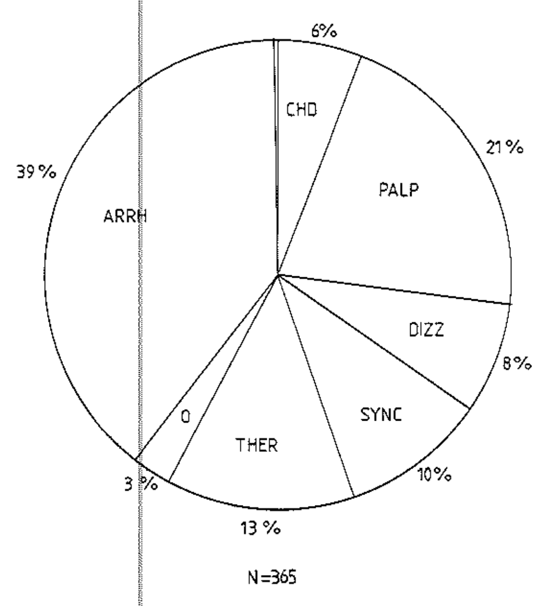


Figure 6.2/1
Distribution of second indications for patients with the indication MI and one other indication. Abbreviations see table 2.2/1. O = Other. The unmarked segment represents the indication evaluation of pacemaker.

procedure was not yet widely recognized. Besides, ambulatory 24-hour ECG-recording had been introduced by Cardiolab as a method to be used in the out-patient clinic. Approximately 30% of patients with the indication MI sustained this MI not more than 3 months before the 24-hour ECG (table 4.1/1).

Considering patients with two indications (see 4.1.1), it was found that in 55% of patients with the indication MI, this indication occurred in conjunction with another indication. In 28% of patients with the indication MI the second indication was palpitations, dizziness, syncope, or evaluation of therapy (figure 6.2/1). These percentages are slightly higher when patients with three or four indications are considered as well.

The above observations emphasize that 24-hour ECG-recordings were not made in unselected post-MI patients but rather in those post-MI patients who needed extra care because they presented with symptoms or did not respond well to therapy.

It has been shown in section 4.1.2 that the age-distribution of patients with the indication MI differs from the age-distributions of patients

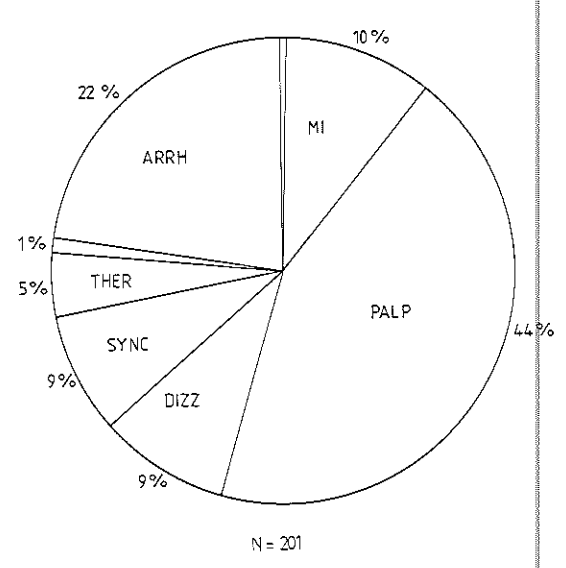


Figure 6.2/2
Distribution of second indications for patients with the indication CHD and one other indication. Abbreviations see table 2.2/1. The unmarked segments represent the indications other (1%) and evaluation of pacemaker.

with other indications. In the age-group 20-29 years MI is scarce compared to other indications. Frequency of occurrence rises with age to a peak between the ages 50-59 (figure 4.1/6A). This is understandable as the incidence of MI may be expected to increase with age. However, this does not explain the marked decrease in the occurrence of the indication MI in the age-groups 70-79 and 80-89. Although the mortality among patients with the indication MI is higher than among patients with other indications (figure 4.2/3), it is unlikely that this large decrease should be accounted for by mortality alone. A similarly peaked age-distribution has been observed in post-MI patients coming to the out-patient clinic of the Thoraxcenter.

6.2.2 coronary heart disease

As with MI the indication 'coronary heart disease' (CHD) refers either to the presence of proved coronary heart disease or only to a suspicion of such illness. Absence of this indication does not guarantee the absence of coronary heart disease in the patient. A glance at table 4.3/1 reveals that the indication CHD and the presence of angina pectoris as reported by the referring physician upon specific questioning are in no way comparable categories.

In 56% of patients with the indication CHD, this indication occurred in conjunction with another indication and in 37% the second indication was palpitations, dizziness, syncope, or evaluation of therapy (figure 6.2/2). This suggests that CHD was usually not the primary indication but was rather an added factor in patients who presented with symptoms. The age distribution of patients with the indication CHD was of the same form as the age distribution of patients with the indication MI (figure 4.1/6A). The remarks made for the latter patient category also apply here. Because mortality is much lower for patients with the indication CHD than for those with the indication MI (figure 4.2/3), mortality can in no way account for the low frequency of occurrence in the higher age groups.

6.2.3 palpitations

Patients with the indication palpitations were more often female (figure 4.1/4) and were younger than patients with other indications (figure 4.1/6B). As a consequence, mortality in patients with the indication palpitations was lower than for patients with any other indication (figure 4.2/3). In fact, patients with this indication had a smaller probability of death within 18 months of ECG-recording than did patients without it (tables 4.3/1 and 4.4/2).

6.2.4 dizziness and syncope

After 'palpitations' and 'evaluation of arrhythmias', 'syncope' is the indication most frequently used for ambulatory 24-hour ECG-recording. Several authors have commented on the importance of ambulatory ECG-recording in patients with syncope or dizziness and also on the need to continue monitoring if a first 24-hour ECG does not yield any results (Walter et al, 1970; Bleifer et al, 1974; Goldberg et al, 1975; Lipski et al, 1976). However, all data in the present study are based on a single 24-hour recording since only first recordings were considered (see 2.3). It is not possible to say for the patients in the present sample how often the alleged symptoms could be satisfactorily explained by the arrhythmias detected on the ambulatory 24-hour ECG.
Inspection of the age distributions shows that patients aged 80-89 more often had the indications 'dizziness' and/or 'syncope' than they did other indications (figure 4.1/6B). The indications 'dizziness' and 'syncope' occurred equally frequently in males and females (fig. 4.1/4).

Mortality was not high as compared with the mortality associated with other indications (figure 4.2/3). At multivariate analysis, the presence of the indications dizziness and syncope did not contribute significantly to the prediction of 18-month mortality.

6.2.5 evaluation of therapy

There were 107 patients in the sample with 'evaluation of therapy' as the only indication and 102 patients who had this indication together with other indications. Sixty of these patients had MI or CHD as a second indication.

Similarly, 20 of the 30 patients in the subsamples of cases and controls with evaluation of therapy as indication had had a previous MI or had suffered from angina pectoris at the time of ECG-recording. Twenty-one of these 30 were using anti-arrhythmic agents and 4 were on beta-blockers. Thus 86% of all patients in the sample with this indication was estimated (by the procedure described in 3.1) to have been on anti-arrhythmic drugs including beta-blockers, while 14% of such patients were not. It is unclear what the physician may have meant by 'therapy' in these instances.

The age- and sex-distributions of patients with this indication (figures 4.1/4,6A) correspond to those of patients with the indications MI or CHD due to the high correlation with these indications.

6.2.6 other

The age-distribution of patients with the indication 'other' showed no important deviations from the form represented in figure 4.1/5. The indication occurred equally often in males and females. Mortality (figure 4.2/3) was higher than in patients with palpitations, dizziness, syncope or the indication CHD.

Explanatory notes which physicians occasionally added for patients with the indication 'other' revealed the presence of such conditions as congestive heart failure, diabetes, hypertension, ventricular or atrial septal defect, epilepsy, cardiomyopathy and coronary artery bypass surgery. This information was not representative for the sample, however, and could therefore not be used in the statistical analysis.

6.2.7 evaluation of pacemaker

Fifty-three patients in the sample had the indication 'evaluation of

Table 6.2/1
Coefficients (b) and test-statistics (Z) of a multivariate equation for the prediction of cardiac death based on age, sex and the presence of a pacemaker.

	b	Z
age (years)	.051	7.27
sex (1=male,0=female)	.972	4.28
pacemaker (1=present,0=absent)	1.232	1.96

coefficients estimated by linear discriminant analysis

pacemaker'. These were primarily elderly patients (figure 4.1/6) both male and female (figure 4.1/4). Mortality was relatively high among these patients (figure 4.2/3). The crude odds ratio associated with this indication was 4.4 (table 4.3/1).

This high risk was partly, but not exclusively (table 6.2/1), due to the higher ages of these patients. Furthermore, patients who continue to have symptoms in spite of the presence of a pacemaker are recommended for ambulatory 24-hour ECG-recording only after other methods of detecting pacemaker malfunction have failed to bring anything to light (Bleifer et al, 1974). Uncertainty as to the cause of symptoms puts these patients at increased risk for unexpected complications. Ambulatory 24-hour ECG-recording has been recommended as it may reveal intermittent pacemaker malfunction (Bleifer et al, 1974) or stimuli which inhibit the pacemaker (Jacobs et al, 1981).

There were 9 controls and 10 cases with a pacemaker in the present study. One man aged 42 had pauses of more than 3 seconds in his 24-hour ECG, clearly indicating pacemaker failure. He survived in the subsequent 3 years, possibly as a consequence of the successful detection of pacemaker malfunction. Of the 10 patients who died, 5 deaths were described by the physician as sudden. Of these, one was described as 'cardiac standstill' and one as ventricular fibrillation. The other three were not specified but may well have been of an arrhythmic nature. One patient died because the pacemaker electrode had perforated the myocardium. Two deaths were said to be caused by acute MI and two by myocardial insufficiency. A poor prognosis for pacemaker patients has also been reported elsewhere (Gould et al, 1978; Ginks et al, 1979). Due to the small number of pacemaker patients in the present sample it was not possible to draw systematic conclusions about patients with this indication. Further study on this subject should be based on a sample of patients with pacemakers and a control sample of patients without pacemakers.

6.3 Prevalence of arrhythmias in the sample

6.3.1 ventricular arrhythmias

Uniform PVCs occurred in over 80% of patients in the sample (table 4.1/6), although they occurred during more than 10% of the recording time in less than half of these patients (table 4.1/7).
The prevalence of uniform PVCs tended to increase with age (table 4.1/6). This tendency was even more marked when non-sporadic uniform PVCs were considered (table 4.1/7). Increasing prevalence with age has also been reported by Hinkle et al (1974). Prevalence of uniform PVCs was greater in men than in women. This was also found by Chiang et al (1969) who used standard ECGs and by Rehnqvist (1978) who used 6-hour monitoring in post-MI patients.
It can be seen from tables 4.3/6 and 4.3/7 that cases and controls with MI had a higher prevalence of non-sporadic uniform PVCs than those without MI. This finding suggests a positive association between occurrence of uniform PVCs and MI which, however, is partly caused by the higher ages of controls with MI compared to controls without MI (figure 4.3/3). However, Ryan et al (1975) have also reported that post-MI patients 'had more frequent ventricular ectopic activity of a more advanced grade' (following the classification by Lown and Wolf, 1971 - see 6.4.2) than did patients with angina pectoris who had not sustained an MI.
Similar associations with age, sex and MI were observed for the 'complex' ventricular arrhythmias (multiform PVCs, doublets, ventricular tachycardia, bigeminy).

6.3.2 supraventricular arrhythmias

Premature supraventricular complexes (PSVCs) were found in 60% of patients in the sample (table 4.1/6), though non-sporadic occurrence was found in only 17% (table 4.1/7). They seemed to be more prevalent in women than in men. Prevalence of PSVCs increased with age and was about the same in patients with and without MI (tables 4.3/6,7). A lack of correlation between PSVCs and presence of CHD was reported by Hinkle et al (1969) who used 6-hour recordings and by Chiang et al (1969) who used standard ECGs. Correlation with age was reported by Chiang et al (1969). Studies by these investigators and by Okajima et al (1960) revealed no difference in prevalence of PSVCs between males and females.

Supraventricular tachycardia (SVT) occurred in 18% of patients in the sample (table 4.1/6). There was no clear sex-difference but prevalence did increase with age. SVT was not associated with MI (tables 4.3/6,7). This is in accordance with evidence presented by Hinkle et al (1969). SVT occurred in 15% of patients with palpitations (table 4.1/9) and in 20% of patients with dizziness and/or syncope (table 4.1/10). These figures were not very different from the prevalence in the sample as a whole.

Sinus bradycardia (i.e. a heart rate <50/min.; table 2.2/1) occurred in 15% of patients (table 4.1/6). There was no consistent relationship with age and sex. It was more prevalent in patients with a history of MI than in those without (table 4.3/6,7) and occurred more often in patients who used digitalis than in patients who did not (table 6.3/1). There was no significant association between the prevalence of sinus bradycardia and the use of any other drugs.

6.3.3 other arrhythmias

The remaining arrhythmias which were considered in table 4.1/6 were nodal rhythm, sinus tachycardia (defined as a heart rate >150/min.),

Table 6.3/1

Association between occurrence of sinus bradycardia and use of digitalis

		cases		controls	
		sinus bradycardia		sinus bradycardia	
		present	absent	present	absent
use of digitalis	present	11	56	10	35
	absent	10	118	53	335

Mantel-Haenszel pooled estimate of odds ratio = 2.01

Mantel-Haenszel chi = 2.38 (p <.01).

atrial fibrillation, first degree AV-block, second degree AV-block, IVCD, sinus arrest, pauses and escapes. The estimated prevalence of each of these arrhythmias in the sample was less than 10%. Due to these small numbers it was difficult to demonstrate relationships with age, sex or history of MI. Patients with sinus tachycardia were relatively young. This is not unexpected, since maximal heart rate decreases with increasing age (Astrand, 1960; Binkhorst et al, 1966). Atrial fibrillation was particularly prevalent in patients over 60 years of age. Ventricular arrest, whether lasting 2 to 3 seconds or more than 3 seconds, was clearly more prevalent in patients with the indications 'dizziness' and/or 'syncope' (table 4.1/10) than in the sample as a whole (table 4.1/6).

6.4 Prevalence of arrhythmias as reported in the literature

When we want to compare the present observations concerning the prevalence of arrhythmias with findings published in the literature, we should be aware (Winkle, 1980a) that studies of this kind vary greatly in terms of

1. patient population sampled
2. duration of ambulatory monitoring
3. definitions of arrhythmia frequencies and complexities

The present study is concerned with 24-hour recordings of symptomatic patients. The term 'symptomatic' here denotes that the decision to record a 24-hour ECG was not made by the investigator but through a patient-physician interaction (see 6.1).
Criteria for the classification of arrhythmias have been given in table 2.2/2. Arrhythmia frequency has been defined in section 3.3.
Less easy to assess is the accuracy with which arrhythmias are detected during the analysis of the ECG-recording. This depends on technical aspects as well as on the attention of the analyst (Hinkle et al, 1967; Winkle, 1980b) and is another source of differences between studies.

6.4.1 prevalence of arrhythmias in symptomatic patients

Few studies are available which report the prevalence of arrhythmias in patient populations comparable to the one which has been studied here. Camm et al (1978) reported on 1000 consecutive 24-hour ECG-recordings but they use such a loose terminology that comparison is virtually impossible.

Table 6.4/1
Prevalence of arrhythmias as reported by Bleifer et al (1974) and in the present study.

	Bleifer 1974	Present study		Bleifer 1974	Present study
Uniform PVCs	41	81	PSVCs	45	60
Multiform PVCs	21	49	SVT	16	18
Doublets	10	26	Atrial fibrillation	4	5
VT	4	10	Nodal rhythm	3	3
Sinus bradycardia	8	15	1° AV-block	2	4
Ventr. or suprav. arrest	4	8	2° AV-block	2	4

Abbreviations see table 2.2/2

Bleifer et al (1974) reported on 1673 10-hour recordings in 1281 consecutive patients who seem comparable to the sample of the present study. Although a distribution is not given, indications are similar to those reported here; there were patients with and without previous MI; 48 patients had artificial pacemakers; 54% were male patients; median age was 65 years. Prevalences as reported by Bleifer et al and as given in table 4.1/6 of this thesis are compared in table 6.4/1. Virtually all figures reported by Bleifer et al are smaller than those found in the present study presumably due to the shorter recording time.

Table 6.4/2
Prevalence of arrhythmias as reported by Lopes et al (1975) and in the present study

	Lopes 1975	Present study
multiform PVCs	44	49
bigeminy	53	16
doublets	44	43
VT	13	10
PSVC	63	60
SVT	35	18

Abbreviations see table 2.2/2

Another study which allows comparison is reported by Lopes et al (1975) and concerns 24-hour recordings of 54 patients with a variety of heart disease. Mean age was 51 years (range 17-83); 83% were males; 26% had proven CHD; 44% received cardiac medication. Figures from this study agree well with those reported in table 4.1/6 (see table 6.4/2). The authors comment on the high prevalence of supraventricular tachycardia they observed and mention that SVT often occurred during sleep, as was also reported by Lown et al (1973). Even so, no satisfactory explanation is given. The remarkably high prevalence of bigeminy also remains unexplained.

6.4.2 ventricular arrhythmias in post-MI patients

Many publications are available reporting prevalence of ventricular arrhythmias in post-MI patients. However, the proportion of patients with 'any PVCs' is related to length of recording time. In post-MI patients, Ruberman et al (1977) found 52% using 1-hour recording, Moss et al (1971) found 72% using 6-hour recordings, DeBusk et al (1980) found 79% using 12-hour recordings. The influence of length of recording time on prevalence in one and the same population has been studied by Lown & Wolf (1971), Lopes et al (1975), Kennedy et al (1978), Thanavaro et al (1980) and Winkle et al (1981).

The proportions of post-MI patients with 'any PVCs' reported by investigators using 24-hour recordings are given in table 6.4/3. These proportions differ from one study to another, reflecting differences between sampled patient populations, which will be reviewed subsequently. Prevalence of PVCs has been found to increase with age (Hinkle et al, 1974), to be higher in males than in females (Rehnqvist, 1978) and to increase after patients who have sustained an acute MI are discharged from hospital (Rehnqvist, 1978; DeCamilla et al, 1980).

It is rarely possible to compare figures for the prevalence of frequent occurrence of uniform PVCs, because different definitions for 'frequent occurrence' have been used by different authors. Several authors use more than 10 uniform PVCs per hour as criterion (Ruberman et al, 1977; Bigger et al, 1978; DeSoyza et al, 1978). However, Moss et al (1977) used >20 per hour, while Lown & Wolf (1971) chose 30 per hour as a cut-off point. The definition used in the present study is the occurrence of uniform PVCs during more than 10% of recording time i.e. during more than 2½ out of 24 hours. This definition is of a different quality as it involves an amount of time during which PVCs occurred rather than a number of PVCs. The term 'non-sporadic' was used to indicate this.

Lown & Wolf (1971) have ordered the ventricular arrhythmias according to the risk of sudden death they supposed was associated with them. A number of investigators have adopted the practice of classifying their patients according to 'highest grade reached' on the scale proposed by Lown & Wolf (Ryan et al, 1975; Schulze et al, 1975; Kotler et al, 1973;

Table 6.4/3
Prevalences of 'any PVCs' and ventricular tachycardia detected in post-MI patients using ambulatory 24-hour ECG-recordings as reported by different investigators.

	Bigger 1978	DeSoyza 1978	Ryan 1975	Schulze 1975	Present study
sample size	100	46	81	36	668
mean age (range)	61(30-90)	54(24-73)	57(31-85)	--	58(25-83)
% males	70	100	100	--	85
pre- or post-discharge	pre	pre	post	pre	post
	%	%	%	%	%
any PVCs	88	70	86	65	94
VT	14	4	20	19	25

Rehnqvist, 1978). From these publications one can obtain figures for the prevalence of 'no PVCs' (the lowest grade, which is complementary to 'any PVCs') and for ventricular tachycardia (the highest grade) but not for the prevalence of arrhythmias in any of the middle grades. This and other limitations of this classification have been discussed by Bigger et al (1977). Another difficulty is that this classification does not include bigeminy, which therefore often goes unreported. However, an advantage is that patients are assigned to mutually exclusive categories in this way. This is not the case when prevalence of each arrhythmia is reported separately as one patient may demonstrate more than one kind of arrhythmia.

In table 6.4/3 prevalences are given of ventricular tachycardia in post-MI patients as reported by different investigators who used 24-hour ECG-recordings. Bigger et al (1978) reported 88% of post-MI patients with PVCs and 14% with ventricular tachycardia (VT). Ryan et al (1975) reported a higher prevalence of VT (20%). As prevalence of VT is higher in males than in females, this difference may be explained by the fact that Bigger et al included 30% women in their sample. Another explanation for the difference may be that Ryan et al studied patients post-discharge. Patients in the study by DeSoyza et al (1978) were somewhat younger than patients in the two previous studies. This may account at least partly for the lower prevalences of PVCs and VT reported by these investigators.

The paradoxical result reported by Schulze et al (1975) of a low prevalence of PVCs and at the same time a high incidence of VT must remain unexplained because no patient characteristics were given in their publication.
The prevalence of PVCs and VT in post-MI patients reported in the present study is higher than any of the figures reported for other samples of post-MI patients. In our opinion this is a consequence of the fact that, contrary to other reports, the present study is not concerned with unselected MI-patients but with those post-MI patients who present with symptoms or do not respond well to anti-arrhythmic therapy (see 6.2.1).
For this reason a higher prevalence of ventricular arrhythmias is not unexpected. The fact that all 24-hour ECGs were recorded post-discharge may also account for the higher prevalence in the present study. Prevalence of doublets (42%) and multiform PVCs (74%) in the present study are also higher than those reported by Bigger et al (36% doublets, 64% multiform PVCs) and DeSoyza (22% doublets).

6.4.3 patients with palpitations, dizziness or syncope.
Goldberg et al (1975) reported on 130 patients with palpitations, dizziness, syncope or a combination of these symptoms. They recorded 278 24-hour ECGs but correctly reported prevalence as proportion of patients, rather than as proportion of recordings as was done by Bleifer et al and Lopes et al. Prevalences of ventricular tachycardia, pauses and atrial

Table 6.4/4
Prevalence of arrhythmias in patients with palpitations, dizziness or syncope as reported by Goldberg et al and in the present study (tables 3.1/9, table 3.1/10).

	Goldberg 1975	Present study palp	Present study dizz/sync
	%	%	%
VT	5	7	9
SVT	44	15	20
Atrial fibrillation	6	5	4
Pauses	9	x	7

x=not reported

fibrillation as observed in the present study (tables 4.1/9-10) agree well with those reported by Goldberg et al (table 6.4/4). However, prevalence of supraventricular tachycardia is lower in the present study. Lipski et al (1976) reported on 55 patients with similar symptoms. However, prevalences of only a few arrhythmias were reported. Comparison is hindered further by differences in definition.

It is not possible on the basis of the data presented in the present study to say how often the alleged symptoms could be satisfactorily explained by the arrhythmias detected on the 24-hour ECG as was attempted by Camm et al (1978) and by Burckhardt et al (1982).

7 DISCUSSION III: PROGNOSTIC FINDINGS

7.1 Prognostic significance of clinical information

It has been shown in chapter 4 that mortality can be predicted on the basis of routinely available information. History of MI was the most important risk indicator, particularly for the prediction of cardiac death (table 4.4/2). When this variable was included in the equation, there was no significant contribution from a variable indicating whether or not the MI occurred within 3 months prior to ECG-recording. Moss et al (1977) hypothesized that the prognostic significance of ventricular arrhythmias detected 5 months after the acute phase of the MI might have less prognostic significance than the ventricular arrhythmias detected pre-discharge. Their suggestion is not based on data of any importance, however, and is denied by the findings of Ruberman et al (1977, 1981) who demonstrated the prognostic significance of ventricular arrhythmias detected at varying intervals after the MI.

In the present study, an excess risk associated with the use of digitalis which was demonstrated. This is not necessarily due to the drug itself. Use of digitalis and diuretics may indicate the presence of congestive heart failure, a feature which we were unable to include in our dataset. Therefore, contrary to Moss et al (1981) and Ruberman et al (1981) we were not able to study the independent contribution to risk of digitalis use conditional on the presence of congestive heart failure.

With equation 2, cardiac death could be predicted with a specificity of 59% at 90% sensitivity. Specificity increased to 72% when ECG-findings were used for prediction in addition to clinical information. Clearly then, routinely available clinical information should not be neglected for the prediction of mortality. However, a meaningful gain can be obtained by considering ECG-findings as well.

7.2 Prognostic significance of ventricular arrhythmias

7.2.1 results from the present study

Uniform PVCs have not been included in any of the prognostic equations in chapter 4.4. In a multivariate equation including the variables age

Table 7.2/1
Coefficients (b) and Z-values of ventricular arrhythmia variables when each is entered into a linear discriminant function for the prediction of cardiac death, which already includes the variables age and sex.

	b	Z	OR
Uniform PVCs	.475	1.49	1.6
Uniform PVCs (non-sporadic)	.934	3.93	2.5
Multiform PVCs	.838	3.44	2.3
Multiform PVCs (non-sporadic)	1.556	4.99	4.7
Doublets	1.164	4.65	3.2
Doublets (non-sporadic)	2.496	5.10	12.1
Bigeminy	.899	3.11	2.5
Runs	1.517	4.62	4.6
D2VT	1.685	5.28	5.4

OR = odds ratio

and sex, the presence of uniform PVCs did not contribute to the prediction of cardiac death (table 7.2/1) in spite of the high odds ratio at univariate analysis (5.0, table 4.3/5). Clearly, the higher prevalence of uniform PVCs in cases compared to that in controls was caused by the higher ages and higher percentage of males among the cases.
The presence of non-sporadic uniform PVCs did make a contribution to prediction when included in a similar equation (table 7.2/1). In fact, the table shows that non-sporadic occurrence of a ventricular arrhythmia was always of greater prognostic significance than occurrence as such, showing that this distinction is meaningful.
When several ventricular arrhythmias are included in one multivariate equation, the coefficients of some variables become smaller than the values given in table 7.2/1. This is due to the strong association between the occurrence of these arrhythmias, by which presence of the one often implies the presence of the other as well. Therefore, knowledge of the presence of one arrhythmia may be sufficient for prediction causing knowledge of the presence of another associated arrhythmia to become unnecessary.
In the present study, inclusion of non-sporadic multiform PVCs, non-

sporadic doublets and ventricular tachycardia caused the coefficients of all other ventricular arrhythmias to become negligibly small. Non-sporadic doublets and ventricular tachycardia were combined into one variable because the Z-value of non-sporadic doublets decreased as non-ventricular arrhythmias were included.
For the same reason, ventricular pauses were no longer important when atrial fibrillation had been included in the equation. Multiform PVCs were similarly associated with the presence of MI and use of diuretics with the presence of ventricular arrhythmias.

In patients without a history of MI all crude odds ratios for ventricular arrhythmias except the one for bigeminy (overall mortality) exceeded 3.0 (table 4.3/7). In patients who did sustain an MI however, none of these odds ratios exceeded 2.3 (table 4.3/6). Multivariate analysis confirmed that in the present data complex ventricular arrhythmias were more powerful predictors of cardiac death in patients without a history of MI (tables 4.4/7,8).

Odds ratios for complex ventricular arrhythmias were higher when only cases with a cardiac cause of death were considered (table 4.3/5). Furthermore, coefficients for complex arrhythmias were higher in multivariate equations predicting cardiac death than in equations predicting overall mortality (tables 4.4/3,4). This implies that the risk of death from other than a cardiac cause associated with complex ventricular arrhythmias is smaller than the risk of cardiac death associated with these arrhythmias and may even be non-existent (Cornfield et al, 1956; see also Breslow & Day, 1980).

7.2.2 results reported for post-MI patients

In 1971, Lown & Wolf suggested that long term ECG-recordings be made in post-MI patients for the detection of what they termed 'transient risk factors' represented by ventricular arrhythmias (see chapter 1).
Since then, many follow-up studies on the prognostic significance of ventricular arrhythmias as detected on long term ECG-recordings have been reported for post-MI patients and have been reviewed recently by Winkle (1980a). At univariate analysis, the presence of non-sporadic and/or complex PVCs increased risk of cardiac death in the majority of these studies. However, multivariate analysis is needed to prove that

Table 7.2/2

Summary of published reports on the prognostic significance of ventricular arrhythmias in post-MI patients.

reference	nr. patients	number of endpoints	multivariate analysis
Ruberman, 1981,1977	1739	349 cardiac deaths 149 sudden deaths[1]	yes
Davis, 1979	940	115 cardiac deaths	yes
Luria, 1976	143	27 cardiac deaths	yes
Rehnqvist, 1978	160	22 deaths&reinfarctions	yes
Moss, 1977	272	18 cardiac deaths	no
Moss, 1974	100	17 cardiac deaths	yes
Bigger, 1978	100	15 cardiac deaths	bi-&tri-variate
Kotler, 1973	160	14 sudden deaths[2]	bivariate
Vismara, 1975	64	12 sudden deaths[3]	no
DeBusk, 1980	90	11 deaths&reinfarctions	yes
Schulze, 1977	81	8 sudden deaths[2]	bivariate
DeSoyza, 1978	56	8 cardiac deaths	no

[1] within minutes [2] within 1 hour [3] within 6 hours

the prognostic significance of PVCs is independent of other clinical variables. An essential condition for the realisation of a satisfactory multivariate analysis is, that it should be based on a sufficient number of patients reaching the endpoint (a cardiac event or cardiac death, Gail et al, 1976).

Only two follow-up studies of post-MI patients have been reported which were based on a large number of cardiac deaths (table 7.2/2). Davis et al (1979) concluded that the presence of any PVCs on a pre-discharge 6-hour ECG-recording was of prognostic significance independent of the occurrence of left ventricular dysfunction in the coronary care unit, of infarct location and of the presence of multiple rather than a single previous MI. Unfortunately, the number of clinical characteristics considered in addition to ECG-findings is rather small. Ruberman et al (1977, 1981) reported that presence of complex PVCs (R-on-T, ventricular tachycardia, pairs, multiform PVCs, bigeminy) detected in a 1-hour

ECG-recording increased the risk of death and sudden death independent of ST-segment depression, congestive heart failure, elevated heart rate, duration of heart disease, use of diuretics, age and elevated blood pressure.
All other reports on the prognostic significance of PVCs in post-MI patients are based on much smaller numbers of cardiac events (table 7.2/2) and multivariate analysis has been applied in four of these studies.
The statistical power of an analysis based on 27 deaths (endpoints) is necessarily small compared with that of a study based on over a hundred deaths. Therefore, at univariate analysis the difference in mortality rate between patients with and without the characteristic under study (here PVCs) must be greater in order for it to be statistically significant.
At multivariate analysis it means that the number of variables that can be included in an equation is limited. This does not invalidate the resulting equation but it does invalidate the conclusion that variables not included in the equation are not of prognostic significance. It may well be that the study sample is simply too small to demonstrate this prognostic significance.

Considerations of statistical power may explain why some authors include 'complex PVCs' in their prognostic equation (Luria et al) while others include 'frequent PVCs' (Rehnqvist). As these variables are strongly associated with each other, it is unlikely that both would be included in a multivariate equation based on a small number of deaths.
Unfortunately, Ruberman et al did not consider PVC-frequency in multivariate analysis while Davis et al used presence of any PVCs without going into further detail. Moss et al (1974) did construct an equation in which several components of ventricular ectopy were included but this analysis was based solely on patients with PVCs. Hence there was no reference-group without PVCs.

In conclusion, we may be convinced of the independent prognostic significance of ventricular ectopic activity as detected by ambulatory ECG-recording in post-MI patients. However, a study (or an analysis of existing data) delineating the role of individual ventricular arrhythmias is still to be awaited.

Moss (1980) reported preliminary results to suggest that early cycle uniform PVCs and multiform PVCs but not frequent PVCs, bigeminy or repetitive PVCs are associated with increased mortality.

7.2.3 results from the present study for post-MI patients

Prevalence of arrhythmias in the post-MI patients in the present study sample was high when compared with prevalences reported in the literature (table 6.4/3). This is caused by a mechanism of patient selection as a result of which post-MI patients in the present study were more often patients with symptoms (see 6.2.1). Because of this mechanism it is understandable that patients with a previous MI were more likely to have arrhythmias than were the patients in studies where all unselected patients with acute MI underwent ECG-recording pre-discharge. This results in smaller differences in the prevalence of arrhythmias between cases and controls (table 4.3/6). Consequently, more statistical power is needed to detect these differences, which in fact determine the strength of the association between arrhythmias and mortality.

The present analysis of post-MI patients was based on 81 cardiac deaths and 85 survivors. Thus, the ratio of controls to cases is 1 and this implies a decrease of statistical power compared to the overall analysis where the corresponding ratio equals 433/123=3.5 (Gail et al, 1976). The above points explain the poor results for post-MI patients which emerge from multivariate analysis (tables 4.4/5-8) with no single variable (except digitalis use) giving a statistically significant contribution to prediction.

7.3 Prognostic significance of non-ventricular arrhythmias

7.3.1 supraventricular arrhythmias

In the past decade, all attention has been focused on the relationship between ventricular arrhythmias and sudden death. Few reports concerning the prognostic significance of PSVCs as detected by ambulatory ECG-recording have been published, as is also observed by Barrett et al (1981). Odds ratios in tables 4.3/5-7 do not suggest a prognostic significance for PSVCs and this impression was confirmed in the multivariate analysis, where no contribution to prediction could be proved for PSVCs. This is consistent with the findings of Hinkle et al (1969).

Non-sporadic occurrence of supraventricular tachycardia was of prognostic significance both at univariate and multivariate analysis (tables 4.3/5, 4.4/3,4).
Atrial fibrillation was more prevalent in cases than in controls. This was even more marked for continuous atrial fibrillation which rarely occurred in controls (table 4.3/5). The prognostic significance of this arrhythmia remained after correction for the higher ages of patients with atrial fibrillation (tables 4.1/6,7) in a multivariate equation (tables 4.4/3,4).
Bleifer et al (1974) state that both non-sporadic supraventricular tachycardia and atrial fibrillation 'are often an electrocardiographic clue to the presence of occult congestive heart failure, pulmonary embolism, pericarditis, or pulmonary infection'. This is confirmed by Barrett et al (1981) who express the view that 'their prognosis cannot be readily dissociated from that of the underlying disease'.

At univariate analysis, both sinus bradycardia and sinus tachycardia indicated a decreased risk of death (tables 4.3/5-7). Sinus bradycardia was included in the prognostic equation for the prediction of overall mortality (tables 4.4/3,4). However, when the analysis was restricted to cardiac deaths only, the coefficient of sinus bradycardia was no longer significantly different from zero.
Sinus tachycardia was not included in the prognostic equation, presumably due to the smaller numbers of patients (particularly cases) with a peak heart rate greater than 150/min. (table 4.3/5).

7.3.2 conduction disturbances
Both first degree AV-block and IVCD were more prevalent in cases than in controls (table 4.3/5). Comparing continuous and non-continuous occurrence in multivariate analysis, continuous first degree AV-block was a more powerful predictor of mortality than non-continuous first degree AV-block, while intermittent IVCD was a more powerful predictor than continuous IVCD. The contribution of intermittent IVCD to the prediction of cardiac mortality disappeared when overall mortality was considered (tables 4.4/3,4).

First degree AV-block is often associated with serious cardiac conditions such as myocarditis and myocardial infarction. During the acute phase of

MI, the occurrence of AV-block is associated with an increased risk of death up to two years after the event (Thygesen et al, 1977; Madsen et al, 1979; Forsberg et al, 1979). Therefore its prognostic significance, as demonstrated in the present study, is not surprising. However, follow-up studies demonstrating a prognostic significance of first degree AV-block occurring in the absence of acute MI have not been reported. Barrett et al (1981) conclude that the presence of first degree AV-block does not increase risk of death in clinically normal individuals but may slightly increase the risk of a subsequent manifestation of CHD.

In persons who had left IVCD on the 12-lead ECG, excess mortality, independent of other risk indicators, has been observed earlier (Coronary Drug Project, 1972; Schneider et al, 1979; Rabkin et al, 1980). Hinkle et al (1969) observed an association of IVCD with mortality using ambulatory 6-hour ECG recordings. There are, however, no studies which confirm the present study's demonstration of the prognostic significance of intermittent IVCD independent of other risk indicators.

7.3.3 other arrhythmias

Ventricular arrests occurred considerably more frequently in cases than in controls. However, at multivariate analysis the contribution of ventricular arrests to prediction disappeared when continuous atrial fibrillation was included in the equation due to a positive association between these two arrhythmias.

Differences in prevalence of escapes or nodal rhythm between cases and controls were more marked for patients with a history of MI than for those without (tables 4.3/6,7).

In the multivariate analysis, the composite variable ESCNR, indicating presence of escapes (either ventricular or supraventricular) and/or nodal rhythm, was a more powerful predictor of mortality than either escapes or nodal rhythm separately. It was decided to group nodal escapes ventricular escapes and nodal rhythm together, because all these arrhythmias occur as a consequence of abnormalities of impulse conduction or excessively slow impulse formation. We are not aware of any publication in which a prognostic significance for escapes or nodal rhythm has been reported.

7.4 Application

With the equations given in section 4.4, it is possible for the physician to give a prognosis for any patient for whom 24-hour ECG-recording is indicated. Equation 2 (table 4.4/2) can be used at the moment the decision to record a 24-hour ECG has been made to estimate the probability of (cardiac) death within 18 months, $P(D|X)$. Equation 4 (table 4.4/4) can be used to estimate that probability once the results of the ECG-analysis are available.

As an example, let us consider a 58-year old male patient from the present study who, after an acute MI, had been treated for congestive heart failure with digitalis and a diuretic and presented with dyspnea. In addition to other investigations, a 24-hour ECG was recorded.

At this point we can use equation 2 (table 4.4/2) to estimate $P(D|X)$, for either cardiac or overall mortality, as shown in table 7.4/1. Although exact values for $P(D|X)$ have been given, table 7.4/2 can be used to transform the sum-score into a probability. The probability of death within 18 months of the ECG-recording for this particular patient is 28.5%. The probability of cardiac death is slightly smaller: 23%.

Table 7.4/1

Estimation of the probability $P(D|X)$ of (cardiac) death within 18 months of ECG-recording for a man of 58 years treated with digitalis and diuretics using equation 2 (table 4.4/2).

	cardiac mortality		overall mortality	
age	58 * .052	= 3.016	58 * .061	= 3.538
sex	1 * .796	= .796	1 * .670	= .670
MI	1 * 1.527	= 1.527	1 * .972	= .972
palpitations			0 * -.586	= 0
digitalis	1 * 1.015	= 1.015	1 * .861	= .861
diuretics	1 * .722	= .722	1 * .833	= .833
constant	-5.856 - 2.447	= -8.303	-5.393 - 2.402	= -7.795
		+		+
	sum-score	-1.227	sum-score	- .921
	P(D|X)	23%	P(D|X)	28.5%

Table 7.4/2
Determination of $P(D|X)$ to the nearest 5% from the sum-score ss.

ss	P(D|X)	ss	P(D|X)
-	0	0	50
-2.94	5	.20	55
-2.20	10	.41	60
-1.73	15	.62	65
-1.39	20	.85	70
-1.10	25	1.10	75
- .85	30	1.39	80
- .62	35	1.73	85
- .41	40	2.20	90
- .20	45	2.94	95
0	50	+	100

Exact values of $P(D|X)$ can be obtained using the formula:
$P(D|X)=e^{ss}/(1+e^{ss})$.

Both these figures are greater than the corresponding mortality rates in the sample which were 4% and 2.5% respectively.

The ECG-analysis for this patient revealed the frequent occurrence of multiform PVCs and doublets, as well as occasional runs of ventricular tachycardia. In addition, non-sporadic PSVCs were detected and sporadic supraventricular tachycardia.

With these ECG-findings, $P(D|X)$ can be estimated using equation 4 (table 4.4/4). Table 7.4/3 shows the calculations, omitting all coefficients which are to be multiplied by zero. The presence of multiform PVCs and PSVCs in the recording is disregarded as these variables do not appear in the equation. Similarly, the sporadic supraventricular tachycardia is disregarded as only non-sporadic supraventricular tachycardia is included in the equation. The presence of non-sporadic doublets and ventricular tachycardia does contribute to the prediction, however.

The result shows an increase of $P(D|X)$ for overall mortality compared to the outcome of equation 2 but a decrease for cardiac mortality.

The latter may seem to contradict common sense as the presence of ventricular ectopic activity in addition to the other features of the patient would seem to increase the risk of cardiac death rather than to decrease it. Less weight is given to these features in equation 4 than in equation 2 while more weight is given to the presence of non-ventricular arrhythmias (table 4.4/4). However, the patient remains at an increased risk of (cardiac) death after the recording of the 24-hour ECG and the latter prediction (based on equation 4) is more accurate than the prediction which was made before the recording (based on equation 2).

One month after the recording of the 24-hour ECG, the patient had ventricular fibrillation and died in the hospital 12 days later.

Table 7.4/3

Estimation of the probability $P(D|X)$ of (cardiac) death within 18 months of ECG-recording for the same patient as in table 7.4/1 but after analysis of the 24-hour ECG using equation 4 (table 4.4/4).

	cardiac mortality	overall mortality
age	58 * .046 = 2.668	58 * .057 = 3.306
sex	1 * .470 = .470	1 * .606 = .606
MI	1 * 2.059 = 2.059	1 * 1.165 = 1.165
digitalis	1 * .891 = .891	1 * .792 = .792
diuretics		1 * .708 = .708
doublets§ and/or VT+	1 * .730 = .730	1 * .634 = .634
constant	-5.997 - 2.447 = -8.444	-5.443 - 2.402 = -7.845
	+	+
sum-score	-1.626	-.634
$P(D\|X)$	16%	35%

+0=absent, 1=present

§0=absent or present in category 1, 1=present in categories 2,3 or 4

Calculations similar to the ones above have been made for patients with other characteristics and the results have been presented in the form of graphs in section 4.5. In theory, $P(D|X)$ can be estimated for patients with any combination of characteristics. In practice, however, certain characteristics will never be found to be present together in the same patient. For example, non-sporadic supraventricular tachycardia cannot be present where atrial fibrillation occurs continuously. Continuous first degree AV-block and IVCD were found to occur together only once in the present data. Escapes occurred together with non-continuous IVCD only twice.

Taking supraventricular arrhythmias as one category and AV-block, IVCD and escapes as another category, the overlap between these categories and ventricular arrhythmia (non-sporadic doublets and/or ventricular tachycardia) was considered (figure 7.4/1). Only 2 patients (1 with previous MI and 1 without) had arrhythmias in all three categories. Ventricular arrhythmia does not uncommonly occur together with arrhythmias in the other categories. Otherwise overlap is small.

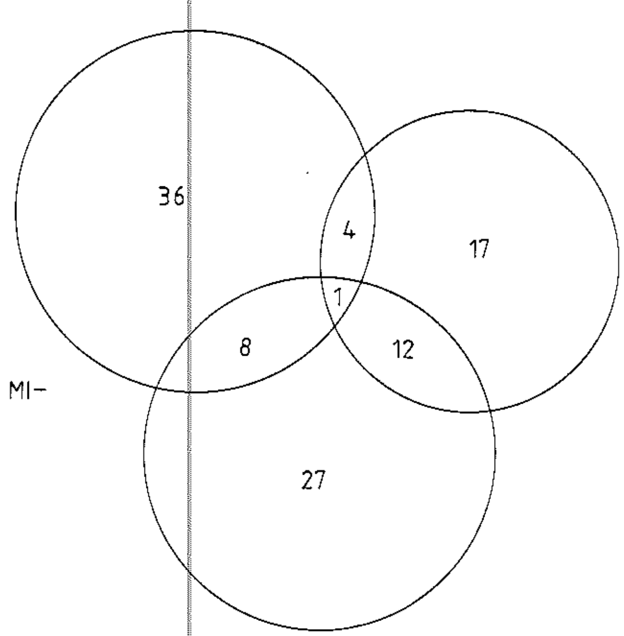


Figure 7.4/1
Venn diagrams showing the number of patients with non-sporadic doublets and/or VT (lower circle), with non-sporadic SVT or continuous atrial fibrillation (upper right), with intermittent IVCD, continuous 1°AV-block or escapes (upper left) and the overlap between these categories.
above: patients without previous MI; below: patients with previous MI.

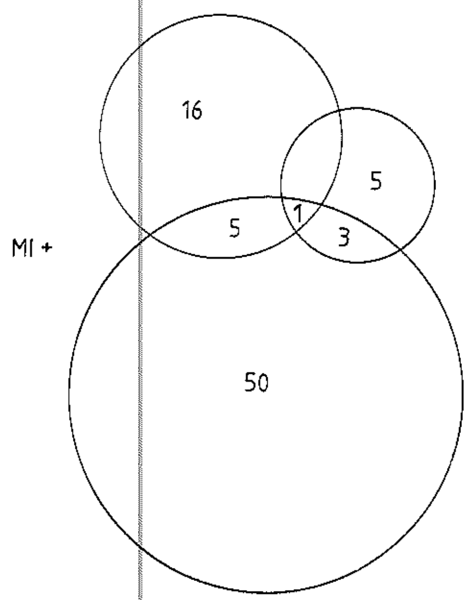


Table 7.4/4

Predicted and observed probability of death in approximate deciles of the predicted probability

$P(D\|X)$ %	number of controls	number of cases	observed mortality rate %
<.1	45	0	0
.1- .2	55	0	0
.2- .3	53	1	.2
.3- .5	75	4	.5
.5- .7	40	3	.7
.7- 1.6	53	7	1.2
1.6- 3.6	42	15	3.1
3.6- 6.7	34	18	4.5
6.7-13.7	23	33	11.3
>13.7	13	42	22.3

As a consequence the maximal possible value of $P(D|X)$ (100%) will only be rarely attained in practice. To illustrate this, deciles of $P(D|X)$ have been approximately determined (table 7.4/4). Only 10% of the 556 cases and controls had a risk of cardiac death greater than 14% and 20% had a risk greater than 7%. The patient just described can be seen to be in the highest decile.

Computing the observed mortality rate in each decile according to the formulas given at the end of section 2.4, shows that there is good agreement between the predicted and the observed probability of cardiac death.

8 SUMMARY AND CONCLUSIONS

8.1 Introduction (chapter 1)

(1.1) After the introduction of the string-galvanometer by Einthoven, various methods for the continuous recording of the ECG were developed.

(1.2) Ambulatory 24-hour ECG-recording has been used for the detection of arrhythmias in clinically normal individuals, in subjects under psychological or physiological stress, in subjects who were asleep, in patients on anti-arrhythmic drug therapy and in patients with cardiac disorders.

(1.3) Cardiolab is a service laboratory located in Rotterdam which distributes equipment for the recording of ambulatory 24-hour ECGs and analyses the recordings centrally. Cardiologists and internists throughout The Netherlands make use of this service and use their own criteria to decide whether or not ambulatory 24-hour ECG-recording is indicated.

(1.4) The present study was designed to investigate whether prognostic information can be derived from a 24-hour ECG which is recorded in the context of usual medical care.
It was concerned with a sample of patients for whom a 24-hour ECG was analyzed by the Cardiolab service.
Through the construction of prognostic equations, it was attempted to identify ECG-findings which would indicate risk of (cardiac) death, given that routinely available clinical information had been taken into account. The resulting prognostic equations permit estimation of the risk of (cardiac) death.

8.2 Methods (chapter 2)

(2.2) Ambulatory 24-hour ECGs were recorded by means of Medilog tape-recorders (Oxford Instruments). The analysis of the tape results in semi-quantitative information as to the frequency with which various arrhythmias occur.

(2.3) Limited information (name, address, date of birth and sex) of

5130 consecutive patients who underwent 24-hour ECG-recording for the first time and were no younger than 10 years was retrieved from the archives of Cardiolab.

(2.5) Survival status of these patients was ascertained at a date at least 18 months after the 24-hour ECG had been recorded.

(2.6) Cases were defined as patients who died within 18 months of the 24-hour ECG. Controls were randomly selected from all patients who survived 18 months.

(2.7) Information pertinent to the time of ECG-recording was collected from the archives of Cardiolab and from the referring physicians for both cases and controls. In addition, the results of the ECG analysis were retrieved. Cause of death was obtained for cases.

(2.4) It is shown that the information available for the cases and controls thus defined (2.6) is sufficient to measure the strength of the association between any patient characteristic and mortality in terms of the relative odds of death. In addition, the risk of death within 18 months of ECG-recording can be estimated for patients with a particular characteristic if the sampling fraction of the controls is known. Hence it is not necessary to collect complete information for all patients in the sample.

8.3 Data analysis (chapter 3)

(3.1) The prevalence of arrhythmias and other patient characteristics in the sample was estimated from the information available for cases and controls on the basis of the stratified sampling scheme. A mutually exclusive classification of indications was devised and this classification was used to explore possible relationships between indication and age by means of Tukey's 'median polish' method.

(3.2) Cumulative mortality was estimated using the method of Kaplan & Meier to take account of patients who were lost to follow-up. The observed number of deaths during the first and second year of follow-up in each of 8 strata of age and sex were compared to the number of deaths expected in each stratum had the age- and sex-specific mortality rates in the sample been equal to the corresponding rates in the Dutch population. The number of deaths per 1000 person-years of follow-up was computed for patients in each category of indication.

(3.3) The proportions of cases and controls with a particular characteristic were tabulated for each available variable. Cases with a cardiac cause of death were considered separately and crude odds ratios were estimated. Notched boxplots were used to compare the age-distributions of cases and controls with or without a history of MI.

(3.4) Multivariate analysis permits correction of the association of one variable with mortality for confounding by a number of other variables. At the same time, the risk of death of patients with a combination of characteristics can be easily estimated. Variables were selected for inclusion into a multivariate prognostic equation for the prediction of mortality by means of linear discriminant analysis. The coefficients in the resulting equation were re-estimated using maximum likelihood. Thus, four multiple logistic regression equations were constructed on the following variables:

equation 1 : age, sex
equation 2 : age, sex, clinical information except ECG-findings
equation 3 : age, sex, ECG-findings
equation 4 : age, sex, clinical information, ECG-findings

Age and sex were always entered into any multivariate equation first and other variables were then included if they contributed significantly to the prediction. The ratio of a coefficient to its standard error was used as a test-statistic.

(3.5) For patients with different characteristics, the risk of death within 18 months of 24-hour ECG-recording can be estimated from the multiple logistic regression equation by computing the sum-score and applying a simple transformation. However, the constant in the equation needs to be corrected.
The estimated probability of death can be used to predict death or survival for each patient. Sensitivity and specificity of this prediction can then be assessed as the actual outcome of follow-up is known for each patient. Receiver Operation Characteristic (ROC) curves represent the sensitivity and specificity of different predictions based on different cut-off values of the estimated probability of death. The ROC curves have been used to compare the performance of the four equations constructed.

8.4 Results (chapter 4)

(4.1) Of the 5130 patients in the sample, 58% were males, 21% sustained a myocardial infarction, 46% did not use any medication and 94% had arrhythmias of one kind or another. Median age in the sample (55) was higher than the median age observed in the Dutch population.

Patients with the indications MI and CHD were predominantly middle-aged. The indication MI occurred more often in males than in females. Patients with the indication palpitations were younger than patients with other indications and were more often female than male. Patients with the indication evaluation of pacemaker were older than patients with other indications.

Eighty-one percent of patients had premature ventricular complexes (PVCs) and 60% had premature supraventricular complexes (PSVCs). Conduction disturbances occurred much less frequently. Prevalence of arrhtyhmias has been estimated in 6 strata of age and sex and in patients with the indications MI, palpitations and dizziness and/or syncope.

(4.2) Mortality was higher in the sample than in the Dutch population, particularly in the lower age-groups. Mortality was highest in patients with the indication MI and lowest in patients with the indication palpitations.

(4.3) Information was available for 195 cases and 433 controls. 123 cases died of a cardiac cause. Median age and the proportion of males were higher in cases than in controls.

(4.4)/ (4.5) It was therefore possible (using equation 1, see 3.4) to predict cardiac mortality on the basis of age and sex alone with a specificity of 41% at 90% sensitivity. Specificity was 59% at the same sensitivity when routinely available clinical information was taken into account. History of MI, use of digitalis and use of diuretics were the clinical variables which contributed significantly to prediction.

When ECG-findings were considered with age and sex (equation 3), specificity rose from 41% to 50% (again at 90% sensitivity). The arrhythmias which contributed to prediction were non-sporadic multiform PVCs, non-sporadic doublets and/or ventricular tachycardia, non-sporadic supraventricular tachycardia, continuous

atrial fibrillation, continuous first degree AV-block, intermittent intra-ventricular conduction defect (IVCD) and escape beats.
When ECG-findings were considered in addition to age, sex and clinical information (equation 4), specificity was 72% at 90% sensitivity. All the variables mentioned above were included in equation 4 except use of diuretics and non-sporadic multiform PVCs

To the prediction of overall mortality, the same variables contributed except IVCD which was not associated with overall mortality and sinus bradycardia and the indication palpitations, which were negatively associated with overall mortality. However, this prediction was less accurate than that of cardiac mortality. When patients with and without a history of MI were considered separately, all the variables included in equation 4 had the same sign in both groups. In patients without a history of MI, most of the characteristics included in equation 4 contributed to the prediction. In patients with a history of MI, however, this was only true for use of digitalis.

8.5 Discussion I (chapter 5)

(5.1) It is shown that the statistical power of an analysis based on all patients in the sample is not much greater than of an analysis based on cases and controls only. It is argued that there are a number of distinct advantages associated with the random sampling of controls over the selection of matched controls.

(5.2) Under-reporting of symptoms by the referring physician cannot have caused the association with mortality of the indication palpitations. Under-reporting of use of medication is unlikely to have caused the association with mortality of digitalis and diuretics. It is also unlikely that bias on the part of the technicians who analysed the 24-hour ECG caused the associations with mortality of any of the arrhythmias included in the multivariate equations.

(5.3) The reliability of the procedure used to estimate the prevalence of arrhythmias in the sample is demonstrated. Limitations and possible alternatives are discussed.

(5.4) The 'median polish' method was used to explore possible relationships between indication and age since it is less sensitive to extreme observations than the usual methods.

(5.5) Estimation of cumulative mortality is accurate within the first 18 months of follow-up but may be slightly overestimated after that time.

(5.6) A degree of arbitrariness is present in any such classification of causes of death. The present classification, though not perfect, may be accepted as being reasonably reliable.

(5.7) In the process of selecting variables for inclusion in the multivariate equations, prior views as to the relative importance of variables and ease of interpretation were considered in addition to statistical significance.
Due to the large numbers of patients involved in the present analysis, the Z-statistic used for significance testing led to the same results as the likelihood ratio test.

(5.8) It is demonstrated that the method used in the present study for the estimation of the sensitivity and specificity of prediction yielded results which do not differ from the results obtained with methods which are theoretically more correct.

8.6 Discussion II (chapter 6)

(6.1) The present sample consists of patients with a variety of cardiac disorders. The results of this study may be influenced by the policy of the referring physicians with regard to the use of 24-hour ECG-recording. In addition, the present results depend on the treatment practices current at the time of the study.

(6.2) Characteristics of patients with different indications have been considered in detail. It was found that a patient might have sustained an MI previous to the 24-hour ECG even though this was not stated as an indication. Recording of a 24-hour ECG was not used as a routine pre-discharge procedure. Instead, post-MI patients in the sample were those who presented with symptoms or did not respond well to therapy. Patients with a pacemaker had the second highest mortality of any category of indication.

(6.3) The present results suggest that the prevalence of ventricular arrhythmias increases with age and is higher in males than in females, as well as higher in patients with a history of MI than in patients without a history of MI. This is consistent with findings reported in the literature.

Prevalence of premature supraventricular complexes (PSVCs) and of supraventricular tachycardia increased with age and was not associated with the presence of a previous MI. This is in agreement with results from other studies. PSVCs occurred more often in females than in males. Sinus bradycardia occurred more often in patients who used digitalis than in patients who did not.

(6.4) Only two publications reporting on the prevalence of arrhythmias are concerned with samples comparable to the sample considered in the present study. Of these two studies, one was based on 10-hour rather than 24-hour recordings while the other concerned only 54 patients. The estimated prevalence of ventricular arrhythmias in patients with the indication MI has been compared with published figures for post-MI patients. Prevalence is higher in the present sample presumably due to the different selection of patients.

8.7 Discussion III (chapter 7)

(7.1) The interval between most recent previous MI and the 24-hour ECG did not contribute to prediction when the presence of a previous MI as such had already been accounted for. It was not possible in the present study to consider the independent contribution of digitalis use to risk conditional on the presence of congestive heart failure.

(7.2) An arrhythmia which at univariate analysis is associated with mortality need not be included in a multivariate equation for the prediction of mortality due to confounding by age, sex or another clinical variable or due to associations with other arrhythmias. A number of studies concerned with the prognostic significance of ventricular arrhythmias in post-MI patients have been reviewed. The present results for post-MI patients do not agree with the results reported earlier due to a different mechanism of patient selection and a lack of statistical power when the present analysis was resticted to post-MI patients only.

(7.3) The various non-ventricular arrhythmias for which a prognostic significance has been demonstrated in the present study can be interpreted as signals of severe underlying disease. For the majority of these arrhythmias, a prognostic significance was not reported earlier.

(7.4) An example is given of the way the multivariate equations given in chapter 4 can be used to estimate the probability of (cardiac) death for a given patient undergoing ambulatory 24-hour ECG-recording.

8.8 General conclusions

This study shows that it is feasible to base an epidemiological investigation on data which have been recorded in the context of usual medical care. However, reliability of the data and mechanisms of patient selection should be carefully considered.

The present study design, in which subsamples are drawn according to outcome of follow-up, allows estimation of the same parameters that can be estimated from a follow-up study based on the entire sample.

A prognostic significance has been demonstrated for both ventricular and non-ventricular arrhythmias detected in ambulatory 24-hour ECGs which were recorded on indication.

The prognostic significance of these arrhythmias was independent of routinely available clinical information.

The prognostic significance of arrhythmias was greater in patients without a history of MI than in post-MI patients. However, post-MI patients in the present sample are not comparable to a sample of patients who are discharged from the coronary care unit after an acute MI.

8.9 Recommendations for further research

In the past decade, much research has been devoted to the prognostic significance of ventricular arrhythmias in post-MI patients. However, it has been shown in the present study that non-ventricular arrhythmias are also of prognostic significance and that this prognostic significance is not limited to patients with a history of MI. Patients in the present sample without a history of MI were often patients with some other cardiac disorder. To delineate the prognostic significance of arrhythmias in patients with different disorders, it will be necessary to follow cohorts of patients with specific disorders and estimate the association of arrhythmias with mortality in such cohorts. Attention should be given to non-ventricular as well as to ventricular arrhythmias. Automated procedures of arrhythmia detection should therefore be extended so that all kinds of arrhythmias can be detected rather than only ventricular arrhythmias as is often the case now.

To gain insight into the quality of the present data, the semi-quantitative information resulting from the analysis of 24-hour ECGs by hand should be compared to the quantitative information resulting from a computer-assisted analysis. It should also be considered whether the accuracy of prediction is improved if it is based on quantitative rather than semi-quantitative information.

The usefulness of the application of prognostic equations in the management of individual patients should be investigated further. The prognostic equations which have resulted from the present study can be used as the basis of a non-experimental study on the efficacy of anti-arrhythmic therapy.

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APPENDIX

Number of patients which each of the hospitals making use of the Cardiolab-service during the study period contributed to the sample.

Number	Hospital
110	Bronovo, 's-Gravenhage
309	Ignatius, Breda
192	Nolet, Schiedam
163	Gasthuis, Middelburg
144	Gemeenteziekenhuis, Schiedam
148	St. Josephziekenhuis, Vlissingen
53	Havenziekenhuis, Rotterdam
177	Ikazia, Rotterdam
128	St. Hippolytus, Delft
149	Holy, Vlaardingen
510	Zuiderziekenhuis, Rotterdam
52	St. Jozefziekenhuis, Gouda
103	Bergwegziekenhuis, Rotterdam
914	Dijkzigt, Rotterdam
214	St. Elisabeth Gasthuis, Haarlem
143	Leyenburg, 's-Gravenhage
95	St. Nicolaas Ziekenhuis, Waalwijk
173	Julianaziekenhuis, Veenendaal
84	Refajaziekenhuis, Dordrecht
69	P. Pauwziekenhuis, Wageningen
124	Oude en Nieuwe Gasthuis, Delft
19	St. Laurensziekenhuis, Breda
58	Diaconessenziekenhuis, Breda
96	Bethelziekenhuis, Delft
35	De Bevelanden, Goes
14	Diaconessenhuis, Leiden
160	Groot Ziekengasthuis, 's-Hertogenbosch
24	St. Antonius Ziekenhuis, Sneek
47	St. Josephziekenhuis, Eindhoven
245	Onze Lieve Vrouwe Gasthuis, Amsterdam
39	Diaconessenziekenhuis, Leeuwarden
34	Catharinaziekenhuis, Eindhoven
33	Julianaziekenhuis, Apeldoorn
35	Carolusziekenhuis, 's-Hertogenbosch
45	Streekziekenhuis, Bennekom
47	Julianaziekenhuis, Ede
99	Majellaziekenhuis, Bussum
45	'De Sionsberg', Dokkum
1	Scheperziekenhuis, Emmen.
5130	

stichting cardiolab

AANVRAAGFORMULIER

Postbus 23220
3001 KE Rotterdam
Telefoon (010) 366988

Naam :
Adres :
Woonpl. :
Telefoon :
Geb. dat. :
Geslacht : m/v
Huisarts :
Part./zkfs.:
Naam verz./zkfs.:
Nummer :

Naam verwijzend arts:

Adres **Telef. nr.:**

Rekening aan: arts/patient/ziekenfonds/ander*
Verwijskaart: ja/neen*

INDICATIE:	Recent Myoc. inf	☐	Palpitaties	☐	Eval. Therapie	☐
	Oud Myoc. Inf	☐	Duizeligheid	☐	Eval. Ritme Strn	☐
	Cor. lijden	☐	Syncope	☐	Eval. Pacemaker	☐
	Andere	☐	zo ja welke			
MEDICATIE:	Digitalis	☐	Anti coag	☐	Diuretica	☐
	B. Blocker	☐	Cor. dilat.	☐	Kalium suppl.	☐
	Anti Arrh.	☐	Anti Hypert	☐	Cholest. verl.	☐
	Andere	☐	zo ja welke			

Telefonisch antwoord gewenst? ja/neen*
Tape registratie: van datum: uur:
tot datum: uur:

Nummer bandje:
Nummer recorder: **Verzonden d.d.** ....

Teststrip bijgevoegd? ja/neen* **Dagboek patient?** ja/neen*

OPMERKINGEN:

kopie zelf houden.

*doorhalen wat niet van toepassing is!

stichting cardiolab

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3001 KE Rotterdam
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VERSLAG RITME TAPE

Naam: Geb. dat.:

Adres: Woonplaats:

Verwijzend arts: Ziekenhuis:

Rekening aan: ziekenfonds/patient/ander:

Datum aanleg: Datum analyse: Analyst(e):

Tape nummer:

kwaliteit: goed: uur, matig: uur, slecht: uur, onbeoordeelbaar: uur

VENTRICULAIRE ARITMIEËN	0	1	2	3	4*)
PVC unf <5/min	☐	☐	☐	☐	☐
PVC unf ≥5/min	☐	☐	☐	☐	☐
Vnt big	☐	☐	☐	☐	☐
PVC mtf <5/min	☐	☐	☐	☐	☐
PVC mtf >5/min	☐	☐	☐	☐	☐
PVC RopT	☐	☐	☐	☐	☐
Vnt dbl	☐	☐	☐	☐	☐
Vnt rit (>100) 3-10	☐	☐	☐	☐	☐
Vnt rit (>100) >10	☐	☐	☐	☐	☐
________	☐	☐	☐	☐	☐

SUPRA VENTRICULAIRE ARITMIEËN	0	1	2	3	4*)
PSVC	☐	☐	☐	☐	☐
Svr rit snl (>100)	☐	☐	☐	☐	☐
Sin rit zsn (>150)	☐	☐	☐	☐	☐
Sin rit trg (<50)	☐	☐	☐	☐	☐
________	☐	☐	☐	☐	☐
________	☐	☐	☐	☐	☐
________	☐	☐	☐	☐	☐

GELEIDINGSSTOORNISSEN	0	1	2	3	4*)
________	☐	☐	☐	☐	☐
________	☐	☐	☐	☐	☐
________	☐	☐	☐	☐	☐

ANDERE ARITMIEËN	0	1	2	3	4*)
________	☐	☐	☐	☐	☐
________	☐	☐	☐	☐	☐
________	☐	☐	☐	☐	☐

*) 0—geen 1—soms 2—matig veel 3—veel 4—continu

AFWIJKINGEN TIJDENS KLACHTEN:

KONKLUSIE: Naam arts:

SAMENVATTING

De stichting Cardiolab distribueert in heel Nederland apparatuur voor de registratie van ambulante 24-uurs ECGs en draagt zorg voor de centrale analyse van deze ECGs. Registratie vindt plaats op indicatie van een cardioloog of internist, b.v. symptomen, evaluatie therapie, myocard infarct (MI) in de anamnese.

Om te onderzoeken of er prognostische betekenis aan deze ECGs kan worden gehecht, werd een steekproef van 5095 patienten vervolgd gedurende tenminste 18 maanden na de ECG-registratie. In die periode overleden 213 patienten (4%) - de 'cases' - waarvan 123 door een cardiale oorzaak. 'Controls' werden gevonden door een aselecte sub-steekproef te nemen uit de patienten die niet overleden waren in die periode.

Voor cases en controls werd informatie verzameld uit het archief van Cardiolab en d.m.v. een enquête bij de verwijzend specialist of huisarts. Deze informatie betrof de anamnese voor en de behandeling ten tijde van de ECG-registratie alsmede de resultaten van de ECG-analyse. Informatie betreffende de aldus gedefiniëerde cases en controls was voldoende om associaties te bestuderen tussen ECG-bevindingen en mortaliteit en maakte het verzamelen van informatie over alle 5095 patienten in de steekproef onnodig.

Prevalentie van aritmieën in de steekproef kon eveneens uit deze informatie worden geschat.

Een multivariate logistische regressievergelijking werd opgesteld om de cardiale mortaliteit te voorspellen op basis van:

1. leeftijd, geslacht
2. leeftijd, geslacht, klinische informatie m.u.v. ECG-bevindingen
3. leeftijd, geslacht, ECG-bevindingen
4. leeftijd, geslacht, klinische informatie, ECG-bevindingen

Klinische informatie die significant bijdroeg aan de voorspelling (vergelijking 2) was aanwezigheid van MI in de anamnese en het gebruik van digitalis en/of diuretica. Ook ECG-bevindingen droegen significant bij aan de voorspelling (vergelijking 3) n.l. de aanwezigheid van: niet sporadische multiforme PVCs, doubletten en/of ventriculaire tachycardie, niet-sporadische supraventriculaire tachycardie, continu atrium-fibrilleren, continu eerste graads AV-blok, intermitterende intra-ventriculaire

geleidings-stoornis (IVCD) en escapes. Wanneer ECG-bevindingen werden beschouwd nadat klinische informatie in rekening was gebracht leverde de aanwezigheid van multiforme PVCs niet langer een bijdrage aan de voorspelling. Het gebruik van diuretica was dan eveneens niet meer van belang.
Aan de overeenkomstige voorspelling van de totale mortaliteit hadden naast de reeds genoemde kenmerken de indicatie 'palpitaties' en de aanwezigheid van sinusbradycardie een significante bijdrage. De aanwezigheid van intermitterend IVCD was voor deze voorspelling niet van belang.
De analyse werd herhaald voor patienten met en zonder MI in de anamnese apart. Het merendeel der genoemde kenmerken had een significante bijdrage aan de voorspelling van de cardiale mortaliteit in patienten zonder MI maar niet in patienten met MI in de anamnese. Dit resultaat komt niet overeen met wat in eerdere studies van post-MI patienten werd gevonden.
Post-MI patienten in de onderhavige steekproef zijn echter niet vergelijkbaar met steekproeven van patienten die uit het ziekenhuis worden ontslagen na het doormaken van een acuut MI.
De opgestelde vergelijkingen kunnen worden gebruikt om de waarschijnlijkheid te schatten van (cardiaal) overlijden binnen 18 maanden na registratie van het ambulante 24-uurs ECG. De uitkomst is geldig voor patienten voor wie ECG-registratie geïndiceerd is en die volgens de huidige (d.w.z. in de studieperiode geldende) inzichten behandeld worden.
Voor alle cases en controls werd de prognose bepaald in termen van overlijden of overleven al naar gelang de geschatte kans op overlijden boven of onder een gekozen grenswaarde viel. Door de voorspelling te vergelijken met de werkelijke uitkomst kon de sensitiviteit en specificiteit van de voorspelling worden geschat. Receiver Operation Characteristic (ROC-) curves geven de combinatie van sensitiviteit en specificiteit bij een gekozen grenswaarde.
Voor de voorspelling van cardiaal overlijden was (bij een sensitiviteit van 90%) bij gebruik van vergelijking 1, 2 en 3 de specificiteit respectievelijk 41%, 59% en 50%. Wanneer voor het bepalen van de prognose klinische informatie wordt aangevuld met informatie uit de ECG-analyse is er een toename van de specificiteit van 59 naar 72%. De overeenkomstige analyse van de totale mortaliteit leidde tot een geringere toename van de specificiteit: van 57 naar 61%.

CURRICULUM VITAE

The author was born December 31, 1953 in Den Haag, The Netherlands. He had his secondary education (HBS-B) at the 'Comenius College' in Hilversum and passed the final examination in 1971. From 1971 to 1978 he studied in the department of Human Nutrition at the Agricultural University in Wageningen with human nutrition and mathematical statistics as major subjects. The research described in this thesis was begun in November 1979 in the Thoraxcenter of the Erasmus University in Rotterdam. At the same time, the author was linked to the Institute of Biostatistics of the Erasmus University.

The International Agency for Research on Cancer of the World Health Organisation has awarded him a fellowship to study epidemiology at the Johns Hopkins School of Hygiene and Public Health in Baltimore, U.S.A.