PREHOSPITAL TRIAGE TO IMPROVE DIAGNOSTIC AND THERAPEUTIC DECISIONS IN PATIENTS WITH SUSPECTED MYOCARDIAL INFARCTION

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PREHOSPITAL TRIAGE TO IMPROVE DIAGNOSTIC AND THERAPEUTIC DECISIONS IN PATIENTS WITH SUSPECTED MYOCARDIAL INFARCTION

Prehospitale triage ter verbetering van de diagnostiek en therapie bij patienten met een mogelijk hartinfarct

Proefschrift

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CONTENTS

INTRODUCTION

The organisation of cardiac assistance for the general practitioner in the municipality of Rotterdam is well organised, due to an intensive co-operation between the general practitioners, the cardiologists, the Central Doktors Laboratorium (S.T.A.R.) and the ambulance department of the Municipal Health Service.

The first initiative towards a more intensive cooperation between cardiologists and general practitioners originated by the inititation of the Imminent Myocardial Infarction Rotterdam (IMIR) study, which started in 1972.[1-3] The study was initiated and executed by the departments of Cardiology and General Practice of the Erasmus University of Rotterdam. In that study, the significance of prodromal symptoms, identified by means of history taking and physical examination, were studied prospectively in patients who visited their general practitioner with symptoms suggestive of myocardial infarction. Detailed history and physical findings were recorded on a standardized questionnaire by the general practitioner. Subsequently, the patient was referred to a special diagnostic centre (the IMIR centre, which was located at the department of Cardiology of the Thoraxcentre of the University Hospital of Rotterdam), where a standard 12-lead ECG was recorded by technicians and blood was drawn for cardiac enzyme determinations (CPK, α-HBDH, SGOT). An additional purpose of the study included the evaluation of this diagnostic centre provided by the study program to the participating general practitioners.

The I.M.I.R. study demonstrated that several variables from a patients history and findings from physical examination were associated independently with increased risk of myocardial infarction. With use of these variables, a predictive model was developed to quantify the risk of myocardial infarction in general practice without laboratory assistance. Unfortunately, implementation of this predictive model in general practice was never realized. Additional results of this study demonstrated that the electrocardiogram contributes considerably to the improvement of the diagnostic accuracy in general practice. The sensitivity of the diagnosis "myocardial infarction" by the general practitioner based on history and physical examination was 44%, and increased to 59% after adding the findings of an electrocardiogram. With the results of the serum cardiac enzyme determinations, the sensitivity increased to 89%.

Thus the I.M.I.R. study confirmed the need of the general practitioners for additional diagnostic information, such as an ECG or cardiac enzyme determinations to increase the diagnostic accuracy in patients with symptoms of chest discomfort.

Consequently, a diagnostic ECG and enzyme service was established and evaluated in the TRACE (Town of Rotterdam Acute Coronary Events) study.[4] The purpose of this study was to test the feasibility of this service, which was made available to all general practitioners in the municipality of Rotterdam. The service was intended for patients with new or worsening complaints, in whom the general practitioner was considering a diagnosis of ischemic heart disease and where he favoured additional diagnostic information on the same day, but for whom immediate hospitalization was felt not to be necessary. This service received the patients at the Central Doctors Laboratorium (S.T.A.R.) or visited non-ambulant patients at home and provided the general practitioner with the results of an ECG and cardiac enzyme determinations (CPK, α-HBDH). Application of the TRACE diagnostic service was feasible and achieved a significant change of policy by the general practitioner. Implementation of this service in general practice resulted in an increase of admissions of patients with evolving myocardial infarction, in whom the diagnosis would have been missed without the additional diagnostic TRACE service. Furthermore, patients without acute cardiac pathology could be exempted from hospitalization. Application of this diagnostic service was safe and was not accompanied with an increased risk of life-threatening complications caused by potential treatment delay of the patient.

While IMIR was designed to identify patients with evolving myocardial infarction, the present Prehospital ECG Project was designed to select patients **without** acute cardiac pathology in whom hospital admission would not be necessary. The methodology and the results of this study are presented in part one of this thesis.

The REPAIR-study (REPerfusion in Acute Infarction Rotterdam) was designed to evaluate the feasibility of initiation of thrombolytic treatment in patients with evolving myocardial infarction before hospital admission.[5-7] The general practitioner who requested hospital admission, or the ambulance-nurse, verified patient eligibility using a short checklist with indications and contra-indications for thrombolytic treatment. A small portable ECG system (Sicard P, Siemens) with a diagnostic computer program was used for analysis and storage of the ECG. The patient was treated with alteplase or streptokinase and transferred to hospital. The methodology and the results of this study are presented in part two of this thesis.

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CHAPTER ONE

OPTIMAL USE OF CORONARY CARE UNITS, A REVIEW

Key words: Acute chest pain- Coronary Care Units- Predictive models

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Introduction

In the early 1960's Coronary Care Units (CCU's) were introduced to ensure prompt response to life-threatening arrhythmias in patients with acute myocardial infarction. After the introduction of thrombolytic therapy in the eighties, treatment of patients with acute myocardial infarction has undergone major change. This therapy has beneficial effects on ventricular function, morbidity and mortality.[1-6] The earlier treatment is initiated the better, which underlines the importance of early diagnosis. Therefore, a rapid evaluation of patients with chest pain and other related symptoms is of paramount importance.

In the Netherlands most patients with acute chest pain or other symptoms first contact their general practitioner. In general practice however, immediate recognition of acute myocardial infarction in patients with chest pain is often difficult. The clinical information available to the general practitioner is often insensitive or nonspecific.[7-9] If the diagnosis is uncertain, general practitioners tend to refer patients to hospitals to "rule out myocardial infarction" rather than risk missing the diagnosis. This strategy ensures a high admission rate for patients with evolving myocardial infarction, but also leads to admission of many patients without acute cardiac pathology (e.g, stable angina pectoris, atypical chest pain). Consequently, in 30-70% of the patients admitted to the CCU with symptoms suggestive of myocardial infarction, this diagnosis is not confirmed.[10] If the differentiation of myocardial infarction and unstable angina pectoris from other causes of chest pain could be improved, the CCU might be utilized more effectivily.

Various strategies have been proposed to increase the efficiency of managing patients with acute chest pain. Some investigators have tried to improve the diagnostic accuracy of the general practitioner.[7,11-13] Others have developed predictive models to identify patients at low risk in the emergency department to minimize unnecessary admissions.[14-24] A third strategy included the creation of a simple observation unit.[25-28] Finally, some investigators have sought to identify patients with good prognosis for early transfer from the CCU to lower levels of care.[29-37] These different approaches will be reviewed in this paper.

Improvement of diagnostic accuracy of patients with chest pain by the general practitioner.

Immediate recognition of myocardial infarction in patients with chest pain is often difficult for the general practitioner, but relatively few data are available on the diagnostic accuracy of predicting acute cardiac pathology in general practice. In the Imminent Myocardial Infarction Rotterdam (IMIR) study, the significance of prodromal symptoms, identified by means of history taking and physical

examination, were studied prospectively in patients with a suspected myocardial infarction.[7] The study population included all patients who contacted their general practitioner with symptoms suggestive of myocardial infarction. The following variables were associated independently with higher risk of myocardial infarction: recent (within 48 hours) onset or worsening of chest discomfort, duration of symptoms of at least 30 minutes, the presence of more than 3 premature ventricular complexes per minute at physical examination, the value of the systolic minus the diastolic blood pressure, and a systolic blood pressure lower than 110 mm Hg. Stabbing pain was negatively associated with the diagnosis of myocardial infarction. With use of these variables, a model was developed to quantify the risk of myocardial infarction in general practice without laboratory assistance. The aim of the IMIR study was to provide guidelines for proper management of patients with symptoms suggestive of myocardial infarction in general practice, rather than make the diagnosis. This study was the first to apply quantative methods in identifying patients with possible myocardial infarction. Regretfully, the results of this study were never formally applied in practice.

Another strategy to improve diagnostic accuracy in general practice is the use of a structured interview by the general practitioner and a computerized out-of hospital ECG, evaluated in the Prehospital ECG Project.[11,12] The Prehospital ECG Project, which is described in detail in chapter 2 and chapter 3 of this thesis, was designed to improve the selection criteria for hospital admission of patients with suspected acute cardiac disease in general practice. The study consisted of two phases. In the first phase, a decision rule was developed to categorize patients into a group at high risk of acute cardiac pathology (myocardial infarction, unstable angina pectoris) and a low risk group (stable angina pectoris, atypical chest pain). In the second phase the decision rule was tested and validated prospectively.

During the first phase, all patients with symptoms of possible cardiac origin, who were seen by a general practitioner and for whom an ambulance was called with the intention to transfer the patient for specialized cardiological evaluation, were eligible. For each patient, the general practitioner completed a standardized questionnaire, that included the history and findings at physical examination. After arrival of the ambulance at the home of the patient, the ambulance-nurse recorded a 12-lead electrocardiogram. In the first phase of the project, all patients were subsequently transported to the hospital. Final discharge diagnoses were obtained from the hospital medical records or the general practitioner. Based on the principal symptoms from history, electrocardiogram and final hospital discharge diagnosis, a decision rule was developed to identify patients in need of immediate hospitalization and those in whom non-admission could be considered. As from 1993, the decision rule has been implemented in Rotterdam. In this second test phase of the Prehospital ECG Project, the general practitioner assessed the probability of acute cardiac

pathology with use of the decision rule. In patients at low risk for acute cardiac pathology, the general practitioner was asked to reconsider the need for immediate hospital admission. In all patients who were not hospitalized, a follow-up visit was made the following day. An additional electrocardiogram was recorded and serum cardiac enzymes were determined to ascertain whether the decision had been correct. The decision rule adviced hospitalization in all patients with a moderate or high probability of acute cardiac pathology. A total of 1020 patients were studied. In 234 patients (23%) the decision rule recommended "no hospitalization". The general practitioner followed this advice in 44% (n=121) of these patients. Among these, 7 patients were diagnosed as having sustained a non Q- wave myocardial infarction, but no complications occurred. The results from this study show that the decision rule can safely reduce the admission rate of patients at low risk of acute cardiac pathology, without increasing the risk of complications for these patients.[11,12]

Improvement of the diagnostic accuracy of acute myocardial infarction in the hospital emergency department.

To achieve more appropriate triage, several algorhythms have been developed to distinguish patients with evolving myocardial infarction and unstable angina pectoris from those with non-urgent or non-cardiac pathology seen at hospital emergency rooms.

Pozen and co-workers developed a predictive instrument, based on 925 consecutive patients seen in the Boston City Hospital emergency room for suspected acute ischemic heart disease.[16] Clinical data and ECG variables possibly related to acute cardiac pathology were collected. In 1980, the predictive instrument was slightly modified, based on data of another 2,320 patients seen in 6 hospitals.[17] The final predictive model included 4 clinical variables and 3 electrocardiographic variables (Table 1). This model generated probabilities of acute cardiac pathology. Implementation of the predictive instrument in the physician's decision making proces did not change the number of CCU admissions of patients with acute cardiac pathology or the number of patients inappropriately sent home from the emergency department. The number of CCU admissions of patients without acute cardiac pathology, however, was reduced by 30% (Table 2).[17]

Goldman et al. developed a computer-derived decision protocol, based on 482 patients observed in the Yale-New Haven Hospital emergency room with chest pain.[14] In 1980, new patients were added to the original cohort and a new computer protocol was designed and validated.[15] Ten distinctive clinical variables from the history and ECG appeared to be independent predictors of myocardial infarction. Again, the number of patients with myocardial infarction correctly admitted to the Coronary Care Unit was not

Tabel 1: Predictive parameters of acute cardiac pathology in previous studies

Variables	Pozen[17]	Goldman[15]	Tierney[18]	Does vd[7]
Age	-	X	0	X
Male gender	-	-	0	X
Presence of:				
Chest pain as main symptom	X	-	X	X
Localisation of pain	X	-	0	X
Radiation of chest pain[1]	-	X	0	0
Duration of symptoms	-	X	0	X
Positive reaction on nitrates	X	-	0	0
No stabbing pain	-	X	0	X
No radiation to back, abdomen	-	X	0	0
Time of onset	-	X	0	X
No pain at palpation	-	X	0	0
Previous history[2]	X	X	X	0
Clammy skin	-	-	-	0
Tachycardia	-	-	-	X
>3 PVC /minute[3]	-	-	-	X
Hypotension	-	-	-	X
				X
ECG abnormalities:				
ST elevation and Q waves	-	X	0	
STT segment changes	-	X	0	
ST depression	X	-	0	
ST elevation	X	-	X	
Abnormal T waves	X	-	0	
Q waves	-	-	X	

X indicates: significant predictor, 0 indicates: no significant predictor, - indicates: not reported.

1 Radiation of pain to left arm, left shoulder or neck
[2] Previous included: myocardial infarction, angina pectoris, PTCA or CABG
[3] PVC denotes Premature Ventricular Complexes

altered after implementation of the predictive model in comparison to the admission rate following the physician's judgement (87.8% vs 88.0%). The number of patients without myocardial infarction admitted to the CCU slightly decreased from 30% to 26% ($p< 0.01$).

In 1982 and 1983, Tierney and colleagues evaluated clinical and ECG data of 540 adults treated in an urban hospital emergency room for acute chest pain in order to derive a decision rule to aid in the diagnosis of myocardial infarction.[18] With the use of the decision rule, the number of patients incorrectly admitted to general wards or sent home increased from 13% to 20%, whereas the number of patients without myocardial infarction admitted to the CCU decreased from 22% to 14%. Aase and co-workers developed a decision support system based on a large number of variables collected from the patients history in the emergency room.[20] During 1982-1983, clinical information was gathered from 918 consecutive patients referred with acute chest pain to the Central Hospital of Akershus. The decision support system correctly classified 92% of patients with acute cardiac pathology (myocardial infarction, unstable angina pectoris) and 84% of patients without acute cardiac pathology. After implementation of the decision rule, the number of patients correctly admitted to the Coronary Care Unit increased from 78% to 88%, whereas the number of patients misallocated to the Coronary Care Unit decreased from 51% to 37%.

Another strategy emphasized the value of Thallium-201 myocardial perfusion scintigraphy in the emergency room of the hospital to select patients for appropriate Coronary Care Unit admission.[21,22] In the study of Wackers et al., 1861 patients were referred to the CCU.[21] In 203 (17%) patients with an atypical history and a non-diagnostic electrocardiogram, Thallium scintigraphy was performed as soon as possible after admission. Thallium results were available within 1.5 - 2 hours after arrival. In retrospect, the results of Thallium scintigraphy showed that 29% of the patients were unnecessarily admitted to the hospital, whereas the percentage of patients inappropriately sent home was 25%. Thus, Thallium scintigraphy may improve efficiency of Coronary Care Unit management. This approach has not been implemented in clinical practice because of organisational restrictions and the high costs of scintigraphy.

Finally, the impact of the use of serum cardiac enzymes in the emergency room on the decision to admit a patient or not, was studied.[23,24] However, in patients with myocardial infarction, cardiac enzymes in the circulation become elevated only after a few hours, while enzymes remain normal in unstable angina. Indeed, in patients who presented within 4 hours after symptom onset, the sensitivity of an elevated total CK was only 38% at a specificity level of 80% while the sensitivity of CK-MB was 34% with a specificity of 88%. The sensitivities of total CK and CK-MB increased in patients who arrived after 4 hours. Thus, the determination of the serum cardiac enzyme levels is useful only after an observation period of several hours.

Table 2: Diagnostic accuracy of the physicians working in the emergency room compared to the accuracy of the predictive models in identifying acute cardiac pathology in patients with chest pain; results of 6 studies.

	Patients with Myocardial Infarction Misallocated to general wards or sent home		Patients without Myocardial Infarction Misallocated to CCU	
First author	Physicians (%)	Computer protocol (%)	Physicians (%)	Computer protocol (%)
Pozen 1980	10	14	20	8
Pozen 1984	7	6	24	17
Goldman 1982	9	9	33	30
Goldman 1988	12	12	30	26
Tierney	13	20	22	14
Aase	17	7	51	37

Short Stay Coronary Observation Unit

Alternatives to Coronary Care Units have been developed for patients at low risk of acute cardiac pathology, to reduce costs and increase the efficiency of hospital admission. Gazpoz and co-workers established a new short stay Coronary Observation Unit, consisting of 2 beds with telemetry monitoring adjacent to the emergency room.[25] The nurse: patient ratio was 1:5, that is similar to the nursing intensity of general medical departments. All patients at low risk of myocardial infarction according to the algorhythm of Goldman[15] and with a normal initial ECG were eligible for admission to the Coronary Observation Unit. Patients were subsequently transferred to the cardiology department if they developed a myocardial infarction or other serious complications. Of 512 consecutive admissions to the Coronary Observation Unit, myocardial infarction was diagnosed in 15 patients (3%), unstable angina pectoris in 28%, while 315 (61%) had a non-cardiac diagnosis. Only 0.4% developed complications. A total of 425 (83%) patients were discharged directly from the Coronary Observation unit. Of this group 1 patient, who left against medical advice, developed a myocardial infarction. Among the others 24% had unstable angina and 68% had non-cardiac pathology. Six months after discharge, the survival rate was 99%. It was concluded that such Coronary Observation Unit is a safe and adequate setting to rule out acute cardiac pathology.

Short stay units have also been acquired at the Academic Medical Centre and the Academic Hospital of the Free University in Amsterdam.[26,27] These facilities were designed to offer rapid access for specialized cardiological evaluation of patients with symptoms which may be caused by myocardial infarction. The patients were referred by the general practitioner, by the emergency room physician or arrived on their own initiative. After an observation period of a few hours a decision was made about the admission policy. Both studies evaluated the prognosis of patients with a diagnosis of "atypical chest pain" who were sent home. After six weeks of follow-up, Koster reported a survival percentage of 99.4% in 460 patients.[26] Similarly, Kooter reported a survival-percentage of 99.5% after 1 year of follow-up in 404 patients.[27]

In the University Hospital of Rotterdam, a Precoronary Care Unit was established in 1976 as part of the Intermediate Care area, consisting of 4 beds with ECG telemetry.[28] In the emergency room, a decision was made for admission on the Coronary Care Unit, the Precoronary Care Unit, or otherwise, based on the findings from history, physical examination and the electrocardiogram. During 6 consecutive months, 174 patients were admitted to the Precoronary Care Unit. Myocardial infarction was diagnosed in 10% of these patients, unstable angina pectoris in 24%, while 53% had other or no acute

pathology. The use of the Precoronary Care significantly reduced the number of CCU admissions of patients who did not have acute cardiac pathology from 22% to 8%, whereas the number of patients with acute cardiac pathology correctly admitted to the Coronary Care Unit increased from 32% to 45%.[28]

Identification of low risk patients for early transfer from the CCU

Rapid identification of patients with chest pain, who are at low risk for acute cardiac pathology and its complications could lead to a shorter observation period in the Coronary Care Unit and earlier transfer to beds outside the Coronary Care Unit. Additional diagnostic information that becomes available after hospital admission can be used to provide early prognostic stratification of such patients. Several studies assessed the feasibility of identifying patients at low risk shortly after admission to the CCU.

Lee developed a strategy to identify patients at low probability of infarction within 12 hours after admission. Patients whose clinical characteristics in the emergency room predicted a low probability of myocardial infarction had only a 0.5 percent risk of infarction if they had neither abnormal levels of cardiac enzymes nor recurrent ischemic chest pain during the first 12 hours of hospitalization.[29] The patients at high probability of myocardial infarction were referred to the CCU within these 12 hours. This study demonstrated that within a 12 hour period after admission, a large group of patients at low risk can be identified on the basis of their emergency room clinical data.

Mulley studied 360 patients admitted after presentation with uncomplicated chest pain.[30] They were categorized into three risk groups on the basis of clinical data collected during the first 24 hours of admission. The low risk group encompassed all patients without major complications, with normal serum cardiac enzymes and a normal electrocardiogram. Only 3 percent of the patients in the low risk group subsequently developed myocardial infarction and 2% had late complications. Identification of low risk patients was feasible and safe and could reduce the total number of days spent in the Coronary Care Unit by 55%.

Slater studied 775 consecutive patients with symptoms suggestive of acute myocardial infarction who were admitted to the Coronary Care Unit after initial screening at the emergency room.[31] In total, 180 patients had no or minimal, nonspecific abnormalities on the entry ECG. Myocardial infarction evolved in 17 (9%) of these patients and 5 (3%) patients developed a major complication. They concluded that the initial ECG can effectively separate patients into a high- and a low risk group for acute cardiac pathology or its complications. Admission to a Coronary Care Unit may not be necessary in the latter group. This was confirmed in the study by Yusuf and co-workers.[34]

Discussion

Patients at low probability of acute cardiac pathology constitute a considerable proportion in many Coronary Care Units, such that physicians should consider more effective alternatives than Coronary Care Unit admission "to rule out myocardial infarction". Different approaches to identify patients at low probability of cardiac pathology were described in this article.

The first strategy aimed to improve the diagnostic accuracy of the general practitioner.[7,11,12] In the I.M.I.R. study, 11 independent variables predicted the probability of myocardial infarction in patients with chest pain. Unfortunately, implementation of this predictive model in general practice was never realized. Still, additional results of this study demonstrated that the electrocardiogram contributes considerably to the improvement of the diagnostic accuracy in general practice. Subsequently, this could be applied in the Prehospital ECG Project, in which a structured interview combined with a computerized electrocardiogram was used in general practice to identify patients with a low probalility of acute cardiac pathology.[11] Application of this predictive model resulted in a reduction of inappropriate hospitalization of low risk patients.

The second strategy encompassed identification of patients with a low probability of acute cardiac pathology in the emergency room of the hospital by using predictive models. Again, application of the algorhythms resulted in a more accurate triage to Coronary Care Units.[14-24]

Alternatives to Coronary Care Units have been developed for patients at low risk of acute cardiac pathology.[25-28] These studies confirmed that an observation period prior to admission to the Coronary Care Unit is a safe approach and will lead to a reduction in unnecessary Coronary Care Unit admission. The success of such Precoronary Care Unit partly depends on its situation in hospital. When the Precoronary Care Units functioned independently, early discharge of low risk patients was facilitated. Establishment of a precoronary care observation unit in the University Hospital Rotterdam-Dijkzigt would be appropriate.

The final approach of rapid identification of patients at low probability of acute cardiac pathology and its complications after a short observation period in the Coronary Care Unit indicated that data collected at admission, particularly serial ECG's and serum enzymes, can be used to identify a subgroup of patients with a low risk of acute cardiac pathology.[29-37] However, a fundamental and practical problem of early transfer of such low risk patients to beds outside the Coronary Care Unit is, in our experience, shortage of beds on the general wards. Rapid transfer to the more economical facilities on the general wards is only possible when enough beds would be available.

Each approach helps to identify patients at low probability of acute cardiac pathology in order to achieve more appropriate triage

to the Coronary Care Units or early discharge. The results of the different approaches apply to the same group of patients with symptoms suggestive of myocardial infarction, in whom a definite diagnosis can not be established in the first instance. Often a combination of various approaches will be most effective. The choice of the most efficient approach will depend on local circumstances. However, if a Pre-Coronary Care Unit could be realized in the emergency department of the University Hospital of Rotterdam, and if the facilities on the general wards could be augmented, both short observation and rapid transferral of low risk patients should lead to more efficient usage of the CCU.

In Dutch practice, many patients primarily contact their general practitioner before they are referred to hospital and therefore the general practitioner is the most important intermediate to select patients with symptoms suggestive of acute cardiac pathology. The Prehospital ECG Project investigated the ability to select patients for hospital admission or stay at their own home, and confirmed the necessity of a computerized ECG for optimum diagnostic accuracy. This appears to be the most effective triage strategy in Rotterdam at this moment. In combination with a triage decision model applied in the emergency room of the hospitals, it may help to optimize use of Coronary Care Units.

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CHAPTER TWO

PREHOSPITAL TRIAGE OF PATIENTS WITH SUSPECTED MYOCARDIAL INFARCTION: EVALUATION OF PREVIOUSLY DEVELOPED ALGORHYTHMS AND NEW PROPOSALS

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Abstract

Objective- To evaluate previously developed algorhythms to improve prehospital triage of patients with suspected acute cardiac disease.
Design- Prospective study.
Subjects- Patients with symptoms of possible cardiac origin, who were seen by a general practitioner and subsequently referred to hospital in the municipality of Rotterdam.
Methods- Prior to hospital admission, symptoms of patients with suspected acute coronary disease were recorded by standardized questionnaire and a computerized ECG was made. All patients were hospitalized and a final diagnosis was established. Algorhythms, proposed by other investigators to distinguish patients with or without acute cardiac disease were tested.
Main outcome measurements- Identification of patients at low (stable angina, atypical chest pain, other pathology) and high (myocardial infarction, unstable angina) probability for acute cardiac pathology.
Results- A total of 1005 patients were studied. 42% had myocardial infarction or unstable angina pectoris. Evaluation of previously developed algorhythms resulted in an unsatisfactory diagnostic accuracy of these strategies in the prehospital setting. In a separate multivariate analysis, 6 characteristics from the history and an electrocardiogram appeared independently and significantly associated with acute cardiac pathology. The presence of an abnormal ECG proved to be the most important predictor.
Conclusions- The hospital based algorhythms were not suitable for prehospital prediction of acute cardiac pathology. A new practical hospital admission model was developed, based on 6 clinical predictors, including analysis of an electrocardiogram. Following appropriate validation, this out-of-hospital protocol may lead to better triage decisions by the general practitioner.

Key words: Hospital admission-Thrombolysis- Myocardial Infarction.

Introduction

Mortality of myocardial infarction is significantly reduced by timely thrombolytic therapy and treatment of life-threatening arrhythmias.[1-5] Thus, rapid evaluation of patients suspected of acute cardiac disease is critically important.[6-12] Accordingly, physicians have adopted a low threshold for referring patients to hospital to " rule out myocardial infarction ".[13-14] While this approach ensures the admission of most patients with true myocardial infarction and other acute cardiac conditions such as unstable angina pectoris, it is also associated with a considerable number of hospital-admissions of patients without acute cardiac pathology.[15-17]

Several algorhythms have been developed using combined clinical and ECG data to distinguish patients with evolving myocardial infarction and unstable angina pectoris from those with less acute or non-cardiac pathology seen at hospital emergency rooms.[18-23] We evaluated these algorhythms in a prehospital setting in the Rotterdam Prehospital ECG Project. On the basis of our findings, an admission procedure for patients with chest pain syndromes is proposed.

Methods

The Rotterdam Prehospital ECG Project builds on the experience with a regional system for prehospital thrombolytic therapy: REPAIR (Reperfusion of Acute Myocardial Infarction in Rotterdam).[10-12] The study involves the ambulance-service of the Municipal Health Department, approximately 300 general practitioners operating in the municipality of Rotterdam, an area of 400 square kilometers with a population of 850,000, and 15 hospitals with 92 Coronary Care beds.

Eligible were all patients with symptoms of possible cardiac origin, who were seen by a general practitioner and subsequently transferred to hospital by the ambulance-service for specialized cardiological evaluation. For each patient, the general practitioner completed a standardized questionnaire, related to the patient's history and findings at physical examination. In addition, the indications and contra-indications for thrombolytic therapy were evaluated.[10-12] The data to be collected included: age, sex, number of hours since the onset of pain, duration and location of the present episode of pain, possible pleuritic or positional components of pain, response to nitroglycerin, the presence of associated symptoms (shortness of breath, sweating or nausea), and previous medical history.

After arrival of the ambulance at the home of the patient, the ambulance-nurse recorded a 12-lead electrocardiogram as previously described.[10-12] In brief, the system employed a small portable battery-powered computer ECG device (Sicard-P, Siemens, Sweden). The ECG electrodes were mounted on a rubber mat, with extremity electrodes positioned at the shoulders and abdomen to ensure rapid placement of the electrodes. The 12-lead ECG was analysed by a computer-

program, developed by Mortara, and stored for later analysis.[24] If the ECG findings were compatible with extensive evolving myocardial infarction, in the abscence of contra-indications, thrombolytic therapy was initiated before hospital transport.[12] After the above assessments, all patients were transported to the hospital.

Final discharge diagnoses were gathered from the hospital medical records. Myocardial infarction was diagnosed when patients met standard history, ECG and enzyme criteria. Unstable angina was defined as a history of angina with increasing frequency and severity of symptoms. In addition, the diagnosis of unstable angina included patients who presented with new recent onset symptoms of angina with subsequent documentation of either ST-T changes at rest, an abnormal stress test or an abnormal coronary arteriogram.

Description and evaluation of decision rules

Previous algorhythms developed to improve the accuracy of the diagnosis of myocardial infarction or unstable angina pectoris are summarized in Table 1.[16-22]

The predictive instrument of Pozen and co-workers was based on 925 consecutive patients seen in the Boston City Hospital emergency room for suspected acute ischemic heart disease. Data from clinical and ECG variables possibly related to acute ischemic heart disease were collected.[20] Between 1979 and 1980, the predictive instrument was slightly modified, based on data of 2,320 patients seen in 6 hospitals.[21]

Goldman et al. developed a computer-derived decision protocol, based on 482 patients observed in the Yale-New Haven Hospital emergency room with a chief complaint of chest pain.[18] In 1980, new patients were added to the original study population and a new computer protocol was devised and validated.[19]

In 1982 and 1983, Tierney evaluated clinical and ECG data of 540 adults treated in an urban hospital emergency room for acute chest pain in order to derive a decision rule to aid in the diagnosis of myocardial infarction.

To evaluate these algorhythms, the same predictors, similar statistical procedures and regression coefficients as well as the same endpoints as described in the original publications were applied in the present prehospital study population. Diagnostic characteristics are presented as sensitivity, specificity, as well as positive and negative predictive value (Table 1). In addition, we constructed a receiver operating characteristic (ROC) curve for each algorhytm based on the actual calculated probabilities. The algorhythms of Goldman were not included in the ROC analysis because of the different statistical approach that was employed.

On the basis of the principal symptoms from history, electrocardiogram and final hospital discharge diagnosis as obtained in our patients, we developed a new model to distinguish patients with low probability for acute cardiac pathology (stable angina pectoris, atypical chest pain, heart failure, rhythm disturbances and other non-cardiac pathology) from those with high probability (myocardial infarction,

Table 1: Variables included in previous decision algorhythms and implemented on the study population

	POZEN[20] 1980	POZEN[21] 1984	GOLDMAN[18] 1982	GOLDMAN[19] 1988	TIERNEY[22]
Study entry	1976-1977	1979-1980	1977	1977,1980	1982-1983
Predicting	AIHD	AIHD	MI	MI	MI
Number of patients	925	2801	482	1379	540
Number of patients with AIHD[1]	-	-	60 (13%)	259 (19%)	62 (12%)
ECG variables:					
ST elevation and/or Q waves	X		X	X	X
ST elevation/depression/straightening[3]	X	X	X	X	
T wave abnormality[4]	X				
Abnormal ECG[5]					
History:					
Pain as most important symptom		X			
Chest pain in lower or midsternum, left arm	X	X			
Pain radiates to neck, left shoulder/arm			X	X	
Pain radiates to back,abdomen or legs				X	
Chest pain is stabbing				X	
Dyspnoe	X				
Duration of chest pain			X	X	
History of NTG use for chest pain[2]	X	X			
Chest pain with sweating/ nausea	X	X	X		X
Prior history of angina and/or MI		X	X	X	X
Pain worse/same than prior angina/MI			X	X	
Chest pain reproduced by palpation			X	X	
Age			X	X	
Sensitivity (%)[6]	56	43	77	74	55
Specificity (%)	61	78	38	40	62
Positive predictive value (%)	74	79	39	39	44
Negative predictive value (%)	41	42	76	75	72

[1] AIHD denotes Acute Ischemic Heart Disease including myocardial infarction (MI) and unstable angina pectoris (UAP).
[2] NTG denotes Nitroglycerin
[3] ST segment with ≥ 1 mm elevation or depression
[4] T waves with peaking or inversion of ≥ 1 mm
[5] ST segment elevation/ depression > 0.25 mm, pathological Q waves, and other anomalies which hindered accurate repolarization interpretation
[6] Sensitivity, specificity and predictive values as determined in the prehospital study population

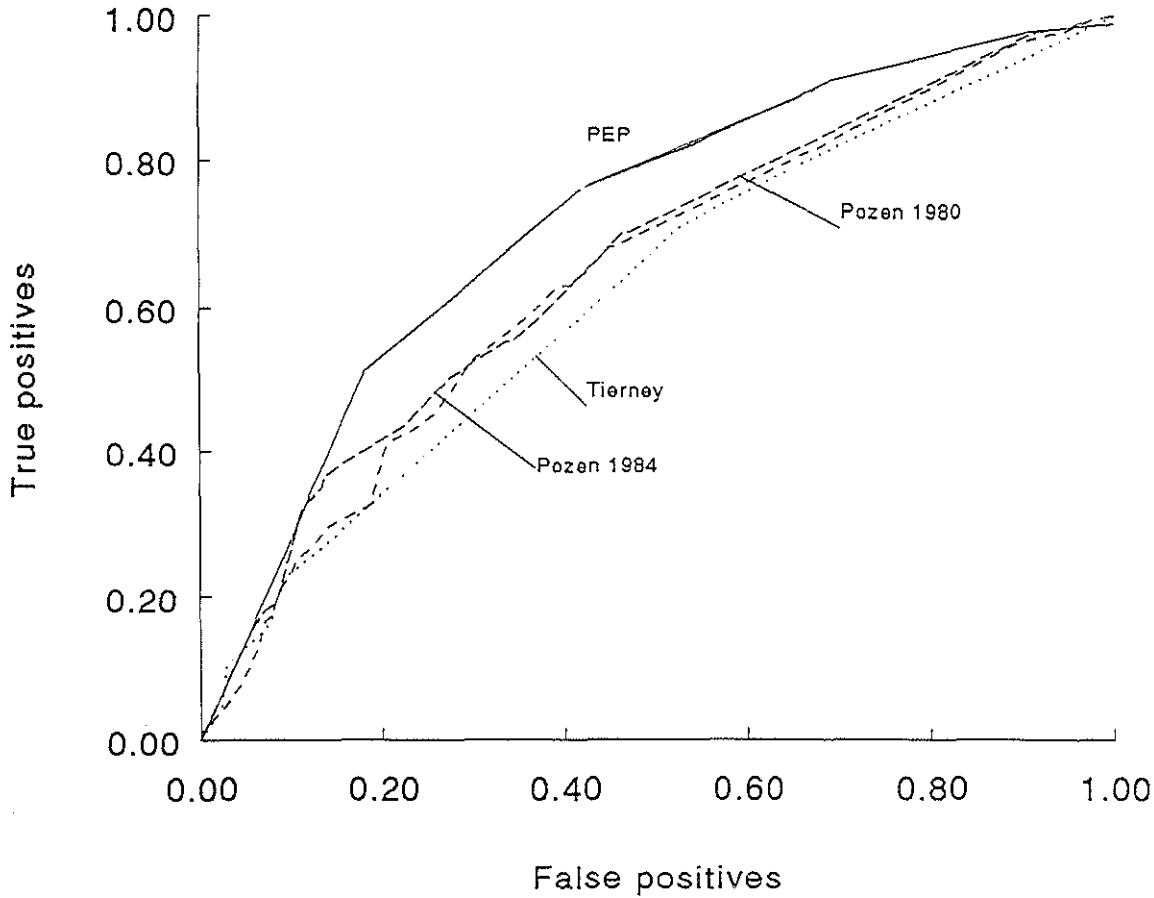

1.00
0.80
0.60
0.40
0.20
0.00
True positives
PEP
Pozen 1980
Tierney
Pozen 1984
0.00
0.20
0.40
0.60
0.80
1.00
False positives

Figure 1

Table 2: Prehospital ECG classification of interpretive statements of the Mortara computerized ECG analysis

ECG classification	ECG criteria
Group 1: Normal or non-specific ECG anomalies	All supraventricular rhythms Atrial enlargement Right ventricular hypertrophy Incompleet right bundle branch block Left anterior or posterior hemi-block Intraventricular conduction delay Junctional / minimal ST depression $\leq$ 0.025 mV
Group 2: Abnormal ECG	Ventricular rhythm Pacemaker rhythm Q waves duration $\geq$ 30 mS Right or left bundle branch block Left ventricular hypertrophy ST elevations $\geq$ 0.05 mV Moderate / marked ST depression > 0.025 mV T wave abnormality of -0.1 mV in $\geq$ 2 leads
Group 3: Extensive myocardial infarction	Sum ST elevation/ depression $\geq$ 1.0 mV in 12 leads in the absence of a bundle branch block[10-12]

unstable angina).

The initial computerized ECG analysis in the REPAIR project was based on the presence or absence of extensive ST segment elevation in order to initiate prehospital thrombolytic therapy and aimed at the identification of patients with definite myocardial infarction.[10-12] In addition new rules were developed to distinguish patients with or without acute cardiac disease. A group of 5 investigators classified all interpretive statements of the ECG computer program into 3 groups with increasing ECG abnormalities (Table 2). The final classification was chosen by a consensus decision of the investigators. Group 1: Normal ECG or non-specific ECG abnormalities, including minor rhythm-, conduction-, or repolarization abnormalities, Group 2: Abnormal ECG. This group included pathological Q waves, more extensive ST segment abnormalities, and in addition all findings that hindered accurate interpretation of the repolarization abnormalities, Group 3: Extensive myocardial infarction, characterized by ST-segment elevations exceeding $\geq$ 0.1 mV in at least two extremity leads or $\geq$ 0.2 mV in the precordial leads with a total sum of ST elevation of 1.0 mV.[10-12]

Data analysis

The univariate relation between the clinical variables and acute cardiac pathology was evaluated with Student-t and chi-square tests. Univariate correlates were entered into a stepwise logistic regression analysis, which identified independent predictors of acute cardiac pathology. The equation for the decision rule was expressed as a logistic regression function:

$P = (1+ \exp -(b_0 + \Sigma\, b_i x_i))^{-1}$

where P is the probability that acute cardiac pathology is present (myocardial infarction, unstable angina), b_0 is a constant, b_i is a regression coefficient or weight corresponding to each clinical variable and x_i are the values of the potentially variables predictive of acute cardiac pathology. For dichotomous variables, the value was set equal to 1 if the condition is present and 0 otherwise. The beta-coefficient was used to calculate the additional probability of acute cardiac pathology. The risk for an individual patient was determined by adding the additional probabilities for each predictor present. The presence of chest pain as main symptom was used as a condition to enter the decision rule.

Receiver operator characteristics (ROC) curves were constructed to determine the ratio of true positives to false-positives at different calculated probabilities. The rate of complications (death, cardiac arrest, ventricular fibrillation and reinfarction) was also determined. Subsequently, a simple decision rule was constructed that segregated patients into three groups with increasing probability of acute cardiac pathology.

Results

During 9 consecutive months, from January 1, 1992 to October 1, 1992, 2,895 patients were transported by the ambulance service with symptoms of presumed cardiac origin. In 1,005 of these (35%), the study questionnaire was completed by the general practitioner and an ECG recorded by the ambulance-nurses. Data were incomplete in 1,890 patients (65%) who were therefore excluded from analysis. The reasons for exclusions are shown in Table 3.

Table 3: Total number of patients transported by the ambulance service with symptoms of presumed cardiac origin.

Total number of patients	2,895	
Exluded from analysis		1,890
Reasons for exclusion		
No ECG available		341 (12%)
- Technical reasons		269
- Poor condition of patient		72
No questionnaire available		922 (32%)
- Free call [1]		189
- Absence of GP[2]		208
- Other[3]		525
No ECG and no questionnaire available		627 (22%)
- Poor condition of patient		189
- Free call[1]		76
- Other[3]		62
Eligible patients	1,005 (35%)	

[1] Hospital admission using the national alarm telephone number
[2] GP = General Practitioner
[3] Administrative reasons, other pathology.

The final hospital discharge diagnoses are presented in Table 4. The final hospital diagnosis was not available in 99 patients, leaving a total of 906 patients for further analysis. Their mean age was 67 years, and 54% were men.

Table 4: Final hospital discharge diagnosis of 1005 patients with complete prehospital evaluation

Diagnosis	Number of patients (%)
Myocardial infarction	299 (30)
Unstable angina	120 (12)
Stable angina	95 (9)
Atypical chest pain	190 (19)
Heart failure	31 (3)
Rhythm Disturbances	61 (6)
Other pathology[1]	110 (11)
Unknown pathology[2]	99 (10)

[1] Other pathology included: all other (non-) acute (non-) cardiac pathology.
[2] Unknown pathology included all patients in whom diagnoses were not available.

Patients with a definite diagnosis of myocardial infarction or unstable angina were more frequently of male gender, had more often chest pain as main symptom, radiation of chest pain to neck, left arm or back, nausea/sweating, a history of cardiovascular disease, and an abnormal ECG (Table 5). Current symptoms were not particularly helpful in distinguishing patients with myocardial infarction or unstable angina from those with other causes of chest pain.

Table 5: Characteristics of patients with high and low probability of acute cardiac pathology in univariate analysis

Symptoms	Myocardial infarction, unstable angina N=419 (%)	Other disease N=487 (%)	Relative risk (95% CI)[4]	
Age > 60 yrs	317 (75)	342 (70)	1.16	(0.98-1.43)
Male gender	255 (61)	229 (47)	1.35	(1.17-1.57)[1]
Chest pain	400 (95)	415 (85)	2.42	(1.56-3.77)[1]
Radiation[2]	372 (89)	388 (80)	1.52	(1.19-1.95)[1]
Localisation	288 (69)	274 (56)	1.15	(0.97-1.36)
Nausea/ sweating	305 (73)	310 (64)	1.31	(1.05-1.57)[1]
Prior disease[3]	258 (62)	245 (50)	2.15	(1.00-4.65)[1]
Abnormal ECG	343 (82)	252 (52)	1.58	(1.44-1.74)[1]

[1] P< 0.05
[2] Radiation to neck, left arm, left shoulder, back
[3] Prior cardiovascular disease: MI, angina pectoris, PTCA, CABG.
[4] CI denotes confidence interval

The results of the evaluation of the previous developed algorhythms in our study population are shown in Table 1. In all analyses, the obtained results deviated significantly from those in the original publications with a universal decrease in diagnostic accuracy. For instance, the sensitivity of the decision rule of Goldman and co-workers[19] in the original setting was 99% at a specificity level of 66%, whereas applied in the prehospital study population these values decreased to 74% and 40%, respectively. The decision rule developed by Pozen and co-workers[21] had a sensitivity of 94% at a specificity level of 83% in the original setting and that of Tierney[22] of 81% and 86%, respectively.

Receiver-operating characteristic curves for the different algorhythms are shown in Figure 1. The area under the curve was 0.65 for both algorhythms of Pozen and 0.62 for the algorhytm of Tierney, indicating mediocre performance of these models in a prehospital setting.

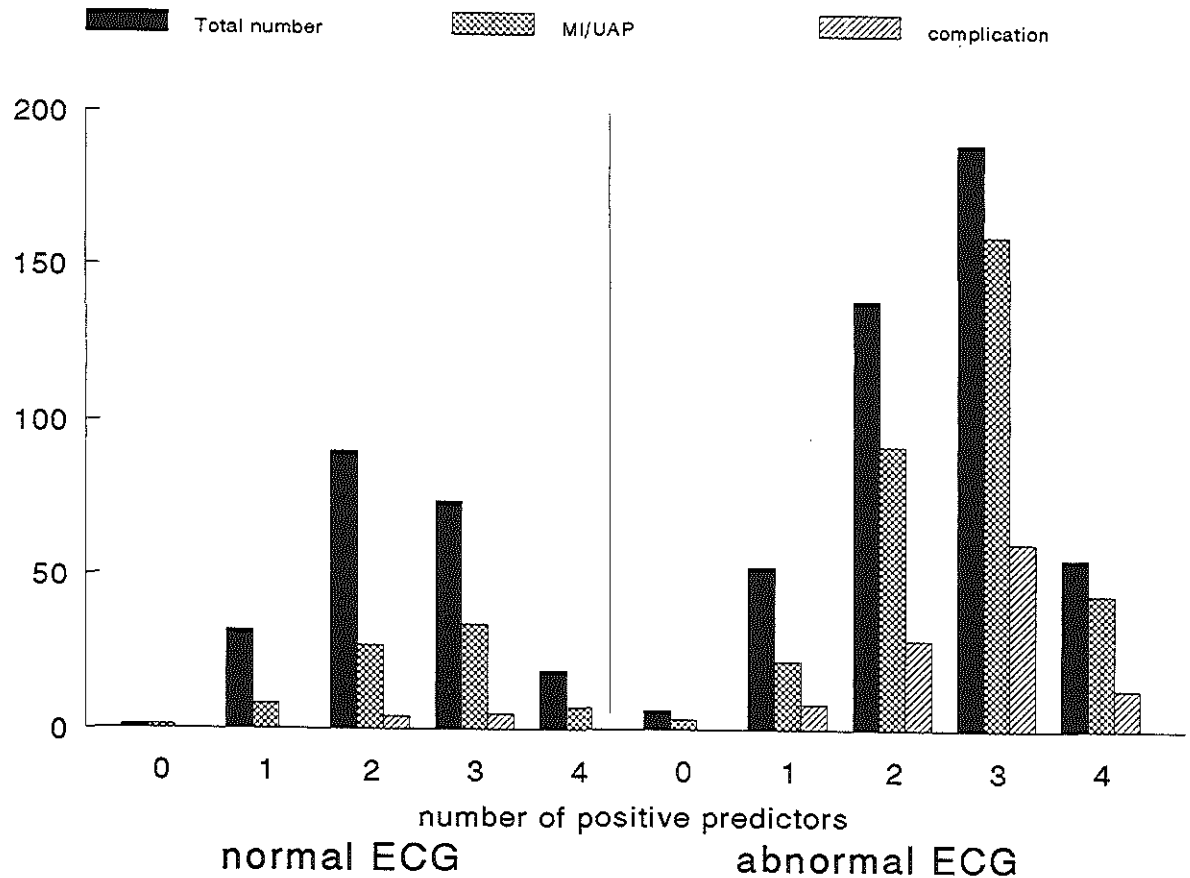
In the multivariate analysis, chest pain as main symptom, male gender, radiation of chest pain, the presence of nausea and/or sweating, a history of prior cardiovascular disease and an abnormal ECG appeared independently and significantly associated with acute cardiac pathology (Table 6).

Table 6: Independent Predictors of Acute Cardiac Pathology in patients with symptoms suggestive of myocardial infarction

Variables	Beta	Odds ratio	95% CI[4]	Probability (%)[3]
Intercept[1]	-2.19			
Abnormal ECG	1.42	4.1	3.0- 5.7	40
Male gender	0.70	2.0	1.5- 2.7	15
Radiation of chest pain to neck, left arm	0.58	1.8	1.3- 2.4	15
Nausea/ sweating	0.58	1.8	1.3- 2.4	15
Prior cardiovascular disease[2]	0.41	1.5	1.1- 2.0	15

[1] Chest pain as main symptom integrated in the intercept.
[2] Prior cardiovascular disease: MI, angina pectoris, PTCA, CABG.
[3] Calculated as additional risk of acute cardiac pathology by using the beta-coefficients of the logistic regression function
[4] CI denotes confidence interval

Figure 2: Total number, number of patients with acute cardiac pathology (myocardial infarction, unstable angina pectoris) and the complications in relation to the number of positive predictors and outcomes of the ECG analysis.



However, the presence of an abnormal ECG proved to be the most important predictor (odds ratio 4.1, 95% confidence interval 3.0-5.7). Exclusion of patients with rhythm disturbances, heart failure or other pathology did not affect the results of the analysis. Based on the results of the multi-variate analysis, the diagnostic properties of clinical predictors combined with the results of the ECG analysis are represented as a ROC curve in Figure 1. The area under the curve was 0.72.

Of the 815 patients with chest pain in the study population, 290 (36%) had a normal ECG and 525 (64%) an abnormal ECG. In both groups, the percentage of patients with acute cardiac pathology and the rate of complications increased with increasing number of positive predictors present (Figure 2). For example, in the presence of two or fewer positive clinical predictors and a normal ECG, 23% of the patients had a final diagnosis of acute cardiac pathology without subsequent complications, whereas the percentage of patients with acute cardiac pathology increased to 37% and the rate of complications to 5% in the presence of at least 3 predictors. As a matter of course, the proportions of acute cardiac pathology and complications was much higher in patients with an abnormal ECG. In that subgroup, only patients without a positive predictor were at low risk for acute cardiac pathology and complications. Based on the findings from the ROC analysis and the prevalence of acute cardiac pathology with accompaning complications in the subgroups, a decision rule was constructed which segregated patients into three groups with increasing risk of acute cardiac pathology and complications (Table 7). By application of the decision rule in the present study population, 167 patients (18%) would be categorised in the "no admission" (4%) or "reconsider admission" (14%) group and they might have been exempted for hospital admission.

Table 7: The final decision rule

No. of Positive Predictors Present at clinical presentation	Normal ECG	Possible or minor MI on ECG	Major MI on ECG[1]
0 Predictor	Home	Reconsider Admission	Always Admission, consider starting thrombolysis
1 Predictor	Home	Admission	
2 Predictors	Reconsider Admission	Admission	
3 Predictors	Admission	Admission	
4 Predictors	Admission	Admission	

[1] Sum of ST elevation/ ST depression $\geq$ 10 mV in 12 leads.

Performance of the decision rule: In patients with a normal ECG and 0 or 1 positive predictor, the decision rule predicts a minimal risk of acute cardiac pathology such that hospital admission is probably not necessary. In patients with a normal ECG and 2 positive predictors or in patients with an abnormal ECG and no positive predictors, the risk of acute cardiac pathology is slightly increased such that the general practitioner may reconsider hospital admission, but hospital admission is not necessary. In all other conditions, hospital admission is recommended.

Discussion

Previous studies have evaluated strategies to improve the accuracy of the diagnosis of myocardial infarction in the hospital emergency rooms in order to reduce the number of unnecessary admissions to the Coronary Care Units. Evaluation of these strategies in a prehospital setting resulted in a decrease of the diagnostic accuracy of these methods in comparison with their initial results. This difference in diagnostic outcomes, however, may be due to patient selection, since our study population differed in major aspects from the previously studied patients. All patients in the Prehospital ECG Project had first contacted their general practitioner and were subsequently referred to the hospital. The other reports included patients who presented themselves at the emergency department. Consequently, the prehospital selection of patients by the general practitioner resulted in a high number of patients with acute cardiac pathology (54%) in the present analysis, in contrast with 13% to 19% in other reports.[18-22]

Furthermore, patients with unstable angina were excluded in the investigations of Tierney,[22] and of Goldman and co-workers[15-16], while all patients with possible myocardial infarction as well as unstable angina were included in this analysis, because both conditions need appropriate recognition and treatment in hospital. It is plausible that the presence of these patients in our analysis have contributed to the lower diagnostic accuracy of previously developed algorhythms.

The outcome of the algorhythm developed in the present study population indicated that predictors of acute cardiac disease in our patients were very comparable to those identified in other studies. We believe therefore that the proposed admission procedure will be robust, although its merits will need to be verified in other settings.

There are relatively few data available on prehospital triage. The Imminent Myocardial Infarction in Rotterdam (IMIR) study assessed the significance of prodromal symptoms, combined with the results from history and physical examination in patients with myocardial infarction.[13] Included were all patients who visited their general practitioner with symptoms suspect of possible cardiac origin. The sensitivity of the diagnosis "myocardial infarction" by the general practitioner based on history and physical examination was 44%, but increased to 59% after adding the findings from an electrocardiogram. While IMIR, as well as previous in-hospital studies, was designed to identify patients with evolving myocardial infarction, the present decision rule was designed to select patients **without** acute cardiac pathology in whom hospital admission would not be necessary. Accordingly, we opted for a high sensitivity (90%) in order to minimize the probability of complications in patients in whom hospitalisation may be avoided as a result of application of the decision rule. It should be emphasized that, in contradiction to the findings of the IMIR study, the physical examination did not contribute to the separation of patients with and without acute cardiac pathology in either of the evaluated studies or in the present analysis. This may be the result of selection bias in our study, because patients with abnormal physical findings, such as heart failure, were referred to hospital by the general practitioner without completion of the prehospital study questionnaire.

Conclusions

This study independently evaluated the merits of previously developed algorhythms for triage of patients with suspected MI. There was major consensus in the determination of the most predictive parameters. On the basis of this analysis as well as on a separate evaluation of findings in our population, a practical hospital admission model was developed, that included 6 characteristics from the history and an electrocardiogram. The ECG proved to be the most important predictor of acute cardiac pathology. Prehospital triage could prevent inappropriate admission of a substantial number of patients at relatively low probability of myocardial infarction or unstable angina. The proposed out-of-hospital protocol could lead to better triage by the general practitioner.

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CHAPTER THREE

IMPLEMENTATION OF A PREHOSPITAL DECISION RULE IN GENERAL PRACTICE: TRIAGE OF PATIENTS WITH SUSPECTED MYOCARDIAL INFARCTION

Key words: Predictive model- Hospital admission- Myocardial Infarction.

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Abstract

Objective- To improve prehospital triage of patients with suspected acute cardiac disease.
Design- Prospective study.
Subjects- Patients with symptoms suggestive of acute cardiac pathology, who were seen by a general practitioner, for whom acute admission into hospital was requested, and in whom a prehospital ECG was recorded by the ambulance service.
Methods- The study consisted of two phases. In the first phase, a decision rule was developed based on clinical characteristics and ECG findings in 1,005 patients with suspected acute cardiac pathology. In the second phase, the decision rule was prospectively validated. Symptoms were recorded by a standardized questionnaire by the general practitioner and a computerized ECG was made by the ambulance nurses at the home of the patient. Three electrocardiographic outcomes were available: "normal ECG", "possible myocardial infarction" or "extensive myocardial infarction". By use of the predictive model, the general practitioner could subsequently decide if hospitalization was necessary or not.
Main outcome measurements- Identification of patients at low (stable angina, atypical chest pain, other pathology) and high (myocardial infarction, unstable angina) probability of acute cardiac pathology.
Results- Among 1,020 patients evaluated in the validation phase of the study, the decision rule recommended "no hospitalization" in 234 patients (23%). The general practitioner followed this advice in 44% of these patients. Although seven of them developed a non Q- wave myocardial infarction, no complications occurred in patients not admitted. Prehospital triage by the general practitioner resulted in a 12% reduction of the number of patients admitted to the Coronary Care Units.
Conclusions- Prehospital triage by the general practitioner was improved using a standardized questionnaire and prehospital electrocardiography, resulted in a reduction in the number of patients admitted to the Coronary Care Unit, and proved to be safe.

Introduction

Many patients are admitted to the Coronary Care Unit with chest pain suggestive of myocardial infarction that is subsequently ruled out. Typically, in more than 50% of patients admitted to the Coronary Care Unit for presumed myocardial infarction, the diagnosis is not confirmed.[1-2]

In the Netherlands, most patients with suspected myocardial infarction are primarily seen by the general practitioner. However, due to the poor predictive value of the clinical information available, recognition of symptoms possibly related to acute cardiac pathology is often difficult for the general practitioner.[3-5] Because of

fear of the consequences of not referring patients with acute cardiac pathology (myocardial infarction, unstable angina pectoris), the general practitioner tends to hospitalize most patients with chest pain. If guidelines could be developed to help general practitioners to distinguish acute cardiac pathology from other causes of chest pain, the number of unnecessary hospital admissions could be reduced considerably.

Previous studies of patients with chest pain in the Emergency Room or Coronary Care Unit attempted to identify diagnostic and prognostic features of acute cardiac pathology.[6-31] Only a few studies have focussed on prehospital identification of chest pain patients with use of an electrocardiogram.[32-34] The purpose of the Prehospital ECG Project was to improve the selection criteria for hospital admission of patients with suspected acute cardiac pathology by increasing diagnostic accuracy. To achieve this, a decision model, including structured questions and findings from a prehospital computerized ECG analysis, was developed and implemented in general practice in Rotterdam.

Methods

The Prehospital ECG Project consisted of two phases. In the training phase a decision rule was developed.[35] In the validation phase this decision rule was applied in general practice and prospectively validated. The outcome of the decision rule enabled the general practitioner to determine the probability of acute cardiac pathology and to reconsider the decision to refer patients to the hospital.

Development of the decision rule

Details about the development of the decision rule were reported elsewhere.[35] In brief, between January 1, 1992 and October 1, 1992, 1,005 patients were evaluated with symptoms suggestive of acute cardiac pathology, who were seen by a general practitioner and for whom a request for referral to hospital in the municipality of Rotterdam was made to the central ambulance post. For each patient, the general practitioner completed a standardized questionnaire, including age, sex, number of hours since the onset of pain, duration and location of the present episode of pain, response to nitroglycerin, the presence of associated symptoms (shortness of breath, sweating or nausea), previous medical history, and findings at physical examination.

After arrival of the ambulance at the home of the patient, the ambulance-nurse recorded a 12-lead electrocardiogram using a small portable battery-powered computer ECG device (Sicard-P, Siemens, Sweden), which was analysed by a computer-program, developed by Mortara (Mortara Inc, Milwaukee, USA), and stored for later analysis.[36] Subsequently, all patients were transported to the

hospital.

Final discharge diagnoses were gathered from the hospital medical records or the general practitioner. Myocardial infarction was diagnosed when patients met standard history, ECG and enzyme criteria. Unstable angina was defined as a history of angina with increasing frequency and severity of symptoms or new onset angina with subsequent documentation of either ST-T changes at rest, an abnormal stress test or an abnormal coronary arteriogram.

Algorhythms previously proposed by other investigators to improve hospital triage of patients with or without acute cardiac disease were tested in this prehospital study population.[11-15] However, this evaluation of these previously developed algorhythms resulted in an unsatisfactory diagnostic accuracy of these strategies in the prehospital setting, mainly as a result of a higher incidence of acute cardiac pathology in our patients. In a multivariable analysis, 6 characteristics from the history as well as the ECG appeared independently and significantly associated with acute cardiac pathology (Table 1). Subsequently, a new practical model was developed that segregated patients into three groups with increasing probability of acute cardiac pathology (Table 2).

Validation phase

The performance of the decision rule was validated in 1,020 consecutive patients with symptoms suggestive of acute cardiac pathology from April, 1993, until April, 1994. The methodology of this phase was similar to that used in the first phase. Symptoms of patients suspected of myocardial infarction were recorded by the general practitioner using a standardized questionnaire and a computerized ECG was made by the ambulance nurses. For practical purposes, the ECG interpretation was restricted to 3 electrocardiographic outcomes which were made available to the general practitioner: "normal ECG", "possible myocardial infarction" or "extensive myocardial infarction, start thrombolytic therapy".

By use of the decision rule, the general practitioner could subsequently decide whether hospitalization was necessary or not. In the presence of unsuitable social circumstances (patient living alone or without telephone) hospitalization was always effected. Patients not admitted were visited at home the next working day, at which occasion blood was drawn for follow-up cardiac enzyme determinations (CPK, CPK-MB, αHBDH) and a follow-up ECG was recorded by technicians of the Central Doctors Laboratorium. The results of this follow-up were immediately provided to the general practitioner. Complications were recorded up to 30 days after the original visit of the general practitioner and the ambulance service. The final hospital discharge diagnoses were gathered from the hospital medical records or from the general practitioner.

Table 1: Independent Predictors of Acute Cardiac Pathology in patients with symptoms suggestive of acute cardiac pathology

Variables	Beta	Odds ratio	95% CI[3]	Probability (%)[2]
Intercept (α)	-2.19			
Abnormal ECG	1.42	4.1	3.0- 5.7	40
Male gender	0.70	2.0	1.5- 2.7	15
Radiation of chest pain to neck, left arm	0.58	1.8	1.3- 2.4	15
Nausea/ sweating	0.58	1.8	1.3- 2.4	15
Prior cardiovascular disease[1]	0.41	1.5	1.1- 2.0	15

[1] Prior cardiovascular disease: myocardial infarction (MI), angina pectoris.
[2] Calculated as additional risk of acute cardiac pathology by using the beta-coefficients of the logistic regression function
[3] CI denotes confidence interval

Table 2: The decision rule

	ECG findings		
No. of positive predictors present at clinical presentation	Normal ECG	Possible or minor MI on ECG	Major MI on ECG[1]
0 Predictor	Home	Reconsider Admission	Always Admission, consider starting thrombolysis
1 Predictor	Home	Admission	
2 Predictors	Reconsider Admission	Admission	
3 Predictors	Admission	Admission	
4 Predictors	Admission	Admission	

[1] Sum of ST elevation/ ST depression $\geq$ 10 mV in 12 leads. MI denotes myocardial infarction.

Performance of the decision rule: In patients with a normal ECG and 0 or 1 positive predictor, the decision rule predicts a minimal risk of acute cardiac pathology such that hospital admission is probably not necessary. In patients with a normal ECG and 2 positive predictors or in patients with an abnormal ECG and no positive predictors, the risk of acute cardiac pathology is slightly increased such that the general practitioner may reconsider hospital admission, but hospital admission is not necessary. In all other conditions, hospital admission is recommended.

Data analysis- Clinical and electrocardiographic characteristics of hospitalized patients were compared with non-hospitalized patients. The association between findings of the decision rule and the subsequent probability of acute cardiac pathology and its complications was assessed using Student-t and chi-square tests for continious or categorical variables, respectively. Two tailed p-values < 0.05 were considered statistically significant. Receiver operator characteristics (ROC) curves were constructed to determine the ratio of true positives to false positives at different calculated probabilities of the decision rule in the training and validation set.

Results

From April 1993 through April 1994, 1,020 consecutive patients with chest pain were evaluated by the general practitioner and a prehospital ECG was made by the ambulance service. We obtained a final diagnosis on 977 patients and these patients constitute the present analysis. Their mean age was 65.6 years, 519 patients (53%) were of male gender, and 597 patients (61%) presented themselves to the general practitioner within 3 hours after the onset of symptoms.

In 750 patients (77%) the decision rule recommended hospitalization while no hospitalization was adviced in 227 patients (23%). The demographic and clinical characteristics of these patients are shown in Table 3. Compared to patients in whom no admission was recommended, patients requiring hospitalization were significantly older (67.0 versus 61.5 years, $P < 0.05$), and more often of male gender (61% versus 37%, $P < 0.05$). In addition, these patients received cardiac medication prior to the chest pain episode more frequently (71% versus 52%), and needed more medication by the general practitioner to relieve the chest pain.

57% of the patients in the hospitalization group had a final diagnosis of acute cardiac pathology (myocardial infarction, unstable angina pectoris), compared to only 18% in the no hospitalization group (Table 4).

The general practitioners did not admit 99 of the 227 patients (44%) in whom the decision rule recommended no hospitalization (Table 3). The non-referred patients were significantly younger, and needed no or less medication to relieve their chest pain. More often the chest pain subsided after the administration of sublingual nitrates. All non-hospitalized patients had a normal prehospital ECG.

Complications up to 30 days after the initial visit of the general practitioner (death, cardiac resuscitation, recurrent chest pain, heart failure, rhythm disturbances) occurred in 35% in the hospitalization group. In the group of patients who were hospitalized by the general practitioner, in spite of the advice of the decision rule (N=128), acute cardiac pathology was confirmed in 25% and

Table 3: Baseline characteristics of patients in whom the decision rule adviced admission or not and of 227 patients in whom the decision rule adviced "no admission" and who were subsequently hospitalized or not by the general practitioner.

	Decision rule		GP decision	
	Hospital (%)	Home (%)	Hospital (%)	Home (%)
Total number	750 (77)	227 (23)	128 (56)	99 (44)
Mean age (yrs)	67.0*	61.5	63.0	59.4*
Male gender	434 (61)*	85 (37)	40 (31)	45 (45)*
Prior cardiac disease	488 (65)	62 (27)	39 (30)	23 (23)
Radiation of pain	541 (72)	101 (44)	64 (50)	37 (37)*
On cardiac medication	530 (71)*	119 (52)	72 (56)	47 (48)
Medication administered by GP	590 (79)*	149 (66)	97 (76)	52 (52)*
Pain subsides with nitrates	276 (37)	86 (38)	57 (45)	29 (29)*
Sweating/ nausea	516 (69)*	93 (41)	61 (48)	32 (32)*
Clammy skin	200 (27)*	32 (14)	22 (17)	10 (10)*
Normal ECG[1]	219 (29)*	131 (58)	120 (94)	99 (100)*

[1] No ST segment abnormalities, no Q waves or other findings that hindered accurate interpretation of repolarization abnormalities.

* $P < 0.05$

Table 4: Final diagnosis and complications in 977 patients in whom the decision rule adviced hospitalization or non-referral and of 227 patients in whom the decision rule adviced "no admission" and who were hospitalized by the general practitioner or not.

	Decision rule		GP decision	
	Hospital (%)	Home (%)	Hospital (%)	Home (%)
Total number	750	227	128	99
Diagnosis				
Myocardial infarction	265 (35)	27 (12)	20 (16)	7 (7)
Unstable angina pectoris	162 (22)	13 (6)	12 (9)	1 (1)
Atypical chest pain	191 (25)	159 (70)	71 (55)	88 (88)
Other[1]	132 (18)	28 (12)	25 (20)	3 (3)
Complications:				
Death	17 (2)	4 (2)	2 (2)	2 (2)
CPR	16 (2)	-	-	-
Recurrent MI	18 (2)	2 (1)	2 (1)	-
Recurrent AP	137 (18)	5 (2)	5 (4)	-
Heart failure	66 (8)	3 (1)	3 (2)	-
Rhythm disturbances[2]	21 (3)	3 (1)	3 (2)	-

[1] Stable angina pectoris, (supra-) ventricular rhythm disturbances, heart failure or other pathology, [2] Included (supra-) ventricular rhythm disturbances. Abbreviations: GP denotes general practitioner, CPR cardiac pulmonary resuscitation.

complications occurred in 11%. Two patients died after hospital admission: one patient died 30 minutes after arrival in hospital as a result of rupture of a dissecting aneurysm and the other patient developed a fatal myocardial infarction 1 hour after arrival in hospital. In the 99 patients staying home acute cardiac pathology was present in 8%. In 7 patients (7%) a non-Q wave myocardial infarction was detected the next working day at the follow-up visit (Table 4). These patients were subsequently hospitalized and no in-hospital complications occurred. No early death occurred, although two patients died at home during follow-up: one patient died of a malignant lung carcinoma 1 week after the original visit of the general practitioner and the other patient developed a fatal pulmonary bleeding 14 days after the visit of the general practitioner. Thus the combination of the judgement of the general practitioner, aided by the decision rule, succeeded in identification of a subgroup of low risk patients in whom immediate hospitalization would not be necessary.

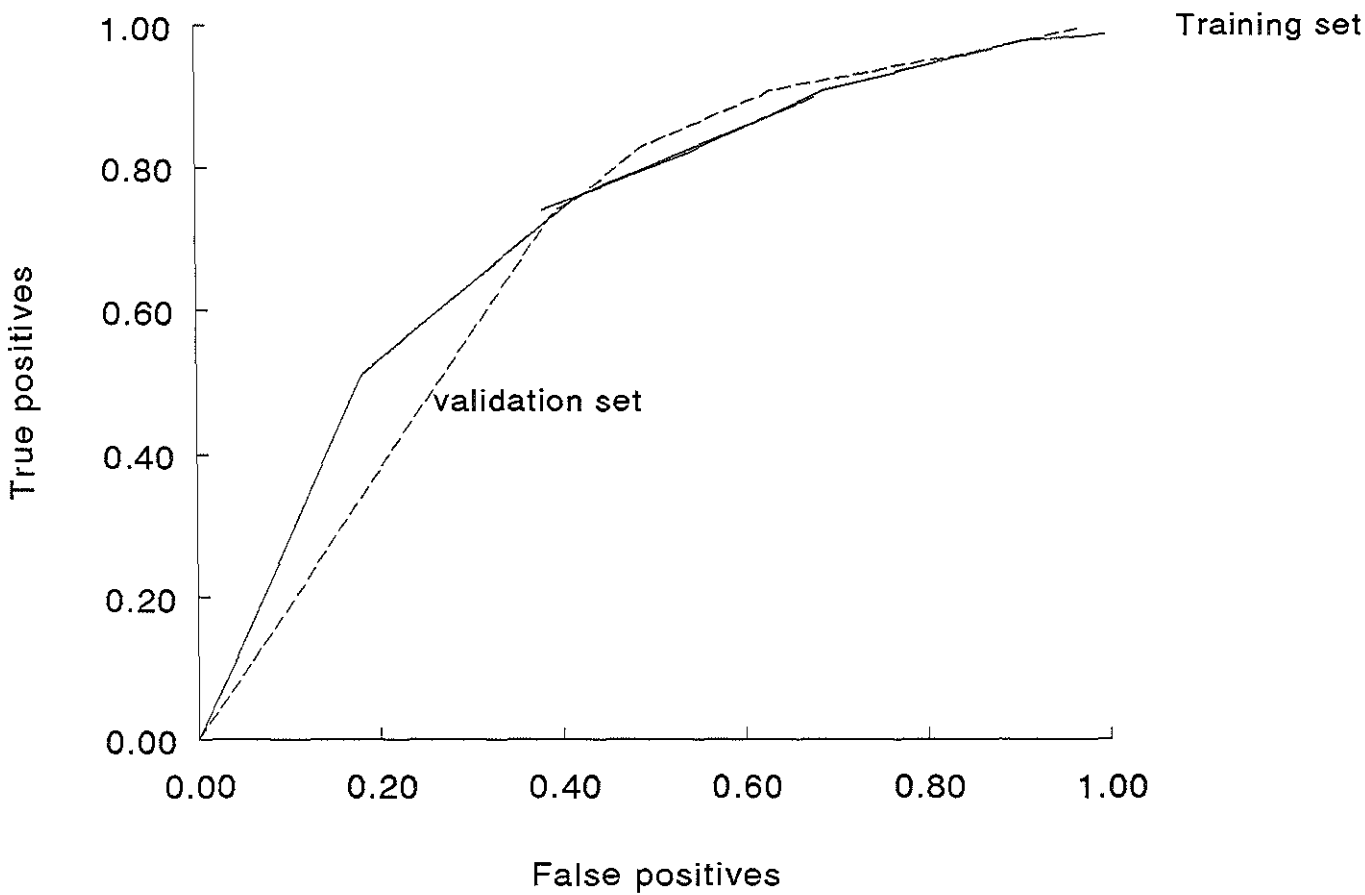
In addition, the general practioners did not admit 19 (2%) of 750 patients for whom the decision rule recommended admission. These patients were significantly younger in comparison with patients who were hospitalized (61.0 versus 67.1 years). Among these patients, 3 patients developed a myocardial infarction, although no life-threatening complications occurred. Of these 19 patients, 13 patients (72%) had a normal prehospital ECG. In the other 6 patients with an abnormal prehospital ECG, the general practitioner decided not the hospitalize these patients because of social circumstances.

Noteworthy, in 95 (79%) of the 121 non-hospitalized patients this decision was made outside the official office hours. The decision not to hospitalize patients was made in 45 patients (38%) by their own general practitioner, whereas in 62% of the cases the decision was made by another general practitioner on duty.

The positive predictive value of the decision rule was 57%. Combined with the general practitioners judgement, the positive predictive value increased to 82%. It is apparent that integrating the judgement of the general practitioner with the predictive model of the decision rule more accurately predicts the probability of acute cardiac pathology and thus the necessity of hospital admission.

Figure 1 shows the receiver-operator curve for the decision rule in the training and the validation phase. The receiver operator curve is a way of representing the overall performance of a diagnostic test and may be used to give the optimal balance between true and false positives. An ideal diagnostic test would have a surface of 100% under the total area of the ROC graph. The area under the ROC curve of the decision rule in the training phase was 0.72. When applied to the validation set, the decision rule discriminated patients with a high and a low probability of acute cardiac pathology with an ROC area of 0.70. This difference was not statistically significant.

Figure 1: Receiver operator characteristics (ROC) curves of the decision rule, determined in the training phase and in the validation phase



Discussion

A decision rule was developed as a diagnostic aid for the general practitioner to improve selection for hospital admission of patients with presumed cardiac pathology. The decision rule provides the general practitioner an estimated risk of acute cardiac pathology and thereby the necessity for hospitalization. The risk is obtained from a structured questionnaire and the analysis of a computerized ECG. Prehospital triage by the general practitioner was practically applicable and resulted in a 12% reduction of the number of patients admitted to the Coronary Care Unit.

The decision rule adviced non-referral in 23% of the patients with chest pain. In 56% of these patients, the general practitioner deviated from this advice and these patients were hospitalized. In this group more acute cardiac pathology and complications occurred in comparison with the non-hospitalized patients. Additional considerations in the general practitioners judgement to hospitalize patients included the amount of medication the patient needed to relieve the chest pain, as well as abnormal findings at physical examination, including a clammy skin or an irregular heart rhythm. Integrating the general practitioners judgement with the outcomes of the decision rule resulted in a more accurate selection for hospitalization of patients with acute cardiac pathology. Therefore, it can be concluded that the decision rule is an important indicator of the probability of acute cardiac pathology and thus the necessity of hospitalization, but additional clinical information is required to optimize the final decision for hospitalization by the general practitioner.

The value of an electrocardiogram for assessment of patients with possible cardiac pathology was already established by findings in the IMIR study[3-5] and in other algorhythms.[11-17] However, procuring an ECG device is not a priority for most general practitioners, since it is often not so easy to make an ECG at the patients home and to maintain the required skills of ECG interpretation. This problem was avoided in the present study by implementing a computerized ECG device in the ambulance-service.

Previous studies have evaluated strategies to improve the accuracy of the diagnosis of myocardial infarction in the hospital emergency rooms in order to reduce the number of unnecessary admissions to the Coronary Care Units.[11-17] Each approach identified patients at low probability of acute cardiac pathology in order to achieve more appropriate triage to the Coronary Care Units. The results are all based on similar patients with symptoms suggestive of myocardial infarction, in whom a definite diagnosis can not be established in the first instance. In the Netherlands, the general practitioner is the most important person to select patients with symptoms suggestive of acute cardiac pathology, because patients primarily contact their general practitioner before they are referred to hospital. The in-hospital based approaches don't tackle the difficult problem of patients who are referred to the hospital and who should not have been there in the first place. The triage in hospital may therefore only minimally reduce the burden on the Coronary Care Units or the Emergency Units.

Consequently, optimal diagnostic accuracy for the general practitioner is the most effective procedure to select patients for hospitalization.

A restriction of our study may be a selection bias in the development of the decision rule, because patients with abnormal physical findings, such as heart failure, were often referred to hospital by the general practitioner without completion of the prehospital study questionnaire during the training phase. On the other hand, patients with myocardial infarction as well as unstable angina were included in the development of the present decision rule, because we are of the opinion that both conditions need appropriate recognition and evaluation in hospital. Patients with unstable angina were excluded in the development of a predictive model in the investigations of Tierney,[15] and of Goldman and co-workers[11-12].

This study demonstrates that a prehospital decision rule can be used as a simple and accurate means to identify patients without acute cardiac pathology and with a low risk of complications. Use of a decision rule in the prehospital setting has two important implications. First, it enables the general practitioner to identify patients with an evolving myocardial infarction in a very early stage, allowing prehospital administration of thrombolytic therapy, which might be of paramount importance in this stage of myocardial infarction. Secondly, the general practitioner is offered the opportunity to reconsider hospitalization to the Coronary Care Units in patients at a low probability of acute cardiac pathology.

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CHAPTER FOUR

COST EFFECTIVENESS ANALYSIS OF OUT-OF-HOSPITAL TRIAGE OF PATIENTS WITH SUSPECTED MYOCARDIAL INFARCTION

Key words: Decision rule- Hospitalization- Economical costs.

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Introduction

In the early 1960's Coronary Care Units (CCU's) were introduced to offer continious cardiac monitoring and to ensure timely response to life-threatening arrhythmias in patients with acute myocardial infarction. After the introduction of thrombolytic therapy in the 1980's, treatment of patients with acute myocardial infarction underwent further changes. This therapy has beneficial effects on ventricular function, morbidity and mortality.[1-6] Treatment benefit is directly related to timely intervention and early diagnosis is of paramount importance. Therefore, rapid evaluation of patients with chest discomfort and other suspected symptoms is critically important. Accordingly, physicians have adopted a low threshold for referring patients to hospital to "rule out myocardial infarction".[7-8] While this approach ensures the admission of most patients with true infarction and other acute cardiac conditions including unstable angina pectoris, it also leads to a considerable number of hospital admissions of patients without actual acute cardiac pathology.[9-11] Typically, in more than 50% of patients admitted to a Coronary Care Unit for presumed myocardial infarction, this diagnosis is not confirmed.[9-10]

Early recognition of patients at low risk for acute cardiac pathology would allow shorter stay in the CCU's or avoidance of hospitalization altogether.[12] We recently reported the results of the Prehospital ECG Project in which the selection criteria for hospital admission of patients with suspected acute cardiac pathology were improved by providing the general practitioner with a structured patient interview and out-of-hospital computerized ECG analysis.[13-14] The present report assesses the economic consequences of this prehospital triage model.

Methods

The Prehospital ECG Project consisted of two phases. In the first phase a decision rule was developed. In the second phase the decision rule was applied in general practice and validated. The use of the decision rule enabled the general practitioner to estimate the probability of acute cardiac pathology (myocardial infarction, unstable angina pectoris) and subsequently to decide whether or not refer patients to the hospital.

Development of the decision rule

The study involved the ambulance-service of the Municipal Health Department, 15 hospitals with 92 Coronary Care beds, and approximately 300 general practitioners operating in the municipality of Rotterdam, an area of 400 square kilometers with a population of 850,000.

Between January 1, 1992 and January 1, 1993, 1,071 patients were evaluated with symptoms of possible cardiac origin by a general practitioner and subsequently referred to hospital by the ambulance-service for specialized

cardiological evaluation. For each patient, the general practitioner completed a standardized questionnaire, related to the patient's history and findings at physical examination. After arrival of the ambulance at the home of the patient, the ambulance-nurse recorded a 12-lead ECG using a small portable battery-powered computer ECG device (Sicard-P, Siemens, Sweden), which was analysed by a computer-program, and stored for later analysis.[15] Subsequently, all patients were transported to the hospital. After initial evaluation of the patient in the emergency room of the hospital, a decision was made upon the necessity of hospital admission. Patients were either discharged home directly from the emergency room or hospitalized.

Based on the results of the history, physical examination, the outcome of the prehospital ECG analysis and the final hospital discharge diagnosis of these 1,071 patients, a hospital admission model was developed. This model segregated patients into three groups with increasing probability of acute cardiac pathology and adviced hospitalization or non-referral. In the presence of two or fewer positive clinical predictors and a normal ECG, the probability of acute cardiac pathology is low and these patients would be categorised in the "no admission" or "reconsider admission" group and they might have been exempted from hospital admission. In patients with more than 2 positive clinical predictors or an abnormal ECG the probability of acute cardiac pathology increased and hospitalization is necessary, according to the decision model.[14]

Prospective application of the algorhythm

The decision rule was validated in a consecutive series of 1,020 patients with chest pain from April 1993, untill April 1994. The methodology was similar to that of the first phase. By application of the decision rule and its recommendations, the general practitioner could now reconsider whether hospitalization was necessary or not. Patients who were not transferred to the hospital were visited at home the following working day by technicians of the Central Doctors Laboratory, at which occasion blood was drawn for follow-up cardiac enzyme determination and a follow-up ECG was recorded. In addition, complications up to 30 days after the initial visit of the general practitioner were established. All other patients were transported to the hospital. Following evaluation of these patients in the hospital emergency room, patients were either discharged from the emergency room or hospitalized.

Economic costs analysis

We compared the costs for each of the two management strategies. The first strategy comprised the admission of all patients to the CCU's, with the exception of patients who were discharged from the emergency room directly. The second strategy included initial triage by the general practitioner using the new decision rule, followed by assessment in the hospital emergency room.

For the present analysis, diagnosis at discharge, and length of stay in hospital were considered.

Results

The number and characteristics of patients with chest pain in the first phase who were hospitalized or discharged directly from the emergency room are given in Table 1. The mean lenght of stay of hospitalized patients amounted to 7.4 days. In total, 100 patients (9%) were discharged directly. These patients were significantly younger. One of them was erroneously discharged with a diagnosis of unstable angina pectoris.

Table 1: Characteristics of patients referred to hospital, who were subsequently hospitalized or discharged from the emergency room in the first phase of the study (N= 1071). Percentages between parentheses.

	Hospitalized	Discharged from emergency room
Total number	971 (91%)	100 (9%)
Mean age (years)	67.3	62.3
Diagnosis:		
Myocardial infarction (%)	297 (31%)	-
Unstable angina (%)	119 (12%)	1 (1%)
Other (%)[1]	555 (57%)	99 (99%)
Complications (%)[2]	204 (21%)	1 (1%)
Mean lenght of stay (days)	7.4	-
Median length of stay (days)	6.0	-

[1] Stable angina, hearth failure, rhythm disturbances, atypical chest pain.
[2] Death, ventricular fibrillation, recurrent chest pain, PTCA, CABG during admission.

Table 2 presents the number and characteristics of patients hospitalized in the second phase of the study. Of 981 patients, 166 patients (17%) were not hospitalized. Of these, 121 (12%) were not hospitalized as a result of the decision rule by the general practitioner and 45 (5%) were discharged home from the emergency room of the hospital. In 10 non-hospitalized patients (8%) a myocardial infarction was detected the next working day at the follow-up visit. These patients were subsequently hospitalized and no in-hospital complications occurred. Two non-hospitalized patients died. The cause of death was non-cardiac and was not related to their non-hospitalization. The mean length of stay of the hospitalized patients was 6.7 days.

Table 2: Characteristics of patients who were referred or not by the general practitioner and the characteristics of referred patients that were subsequently hospitalized or discharged from the emergency room in the second phase of the study (N= 981). Percentages between parentheses.

	Referred by GP Hospitalized	Referred by GP Discharged from emergency room	Not referred by GP
Total number	815 (83%)	45 (5%)	121 (12%)
Mean age (years)	66.7	52.4	58.0
Myocardial infarction	281 (34%)	-	10 (8%)
Unstable angina	172 (21%)	-	1 (1%)
Other[1]	357 (44%)	44 (98%)	110 (91%)
Unknown	5 (1%)	1 (2%)	-
Complications[2]	191 (23%)	-	2 (2%)
Mean lenght of stay	6.7	-	-
Median length of stay	5.0	-	-

[1] Stable angina, hearth failure, rhythm disturbances, atypical chest pain.
[2] Death, ventricular fibrillation, recurrent chest pain, PTCA, CABG during admission.
Abbreviations: GP denotes general practitioner

The economical costs of the two different admission policies are shown in Table 3. The prices for admission on the CCU or general ward were estimated at Dfl 832,50 per day and the costs for evaluation in the emergency room at Dfl 115 (including laboratory tests, ECG and chest X-ray). The average length of stay in hospital of all patients was estimated at 7 days (mean length of hospitalization in the first and second study phase). There was a slight decrease in length of stay of hospital admission between the first and the second study phase, but this is probably a result of changes in course of time and not a result of different study populations. Finally, the total costs per 100 patients were calculated. These amounted to Dfl 525.625 per 100 patients in the first phase of the study and to Dfl 484.253 per 100 patients in the second phase. Additional costs in the second study phase consisted of the recording of a prehospital ECG and the instructions required for the ambulance nurses to apply the computerized ECG recording into practice. These extra costs amounted to Dfl 1.740. A benefit of Dfl 39.632 per 100 patients was obtained with the additional triage decision of the general practitioner. This implies that a significant amount of money was economized by the introduction of the prehospital ECG analysis system.

Table 3: Economical costs in the first and second phase of the study.

	Phase 1	Phase 2
No admission by GP	-	12.4%
ER discharge	10.0%	4.6%
Hospital admission	90.0%	83.0%
Total admission costs (Dfl)		
Home	-	-
ER	115	115
Admission	5.828	5.828
Diagnosis per 100 patients		
Myocardial infarction	28	30
Unstable angina pectoris	11	18
Other[1]	61	52
Costs per 100 patients (Dfl)		
Home	-	-
ER	1.150	529
Admission	524.475	483.724
Total	525.625	484.253
Extra costs per 100 patients (Dfl)		
ECG device	-	1.500
Instructions	-	240
		1.740
Total costs (Dfl)	525.625	485.993
Difference/ 100 patients (Dfl)		39.632

[1] Stable angina, hearth failure, rhythm disturbances, atypical chest pain.
Abbreviations: GP denotes general practitioner, ER emergency room.

Discussion

On the basis of our analysis, it appears to be cost effective to provide prehospital ECG analysis and a structured questionnaire to the general practitioner. Implementation of the decision rule in general practice resulted in a 12% reduction of the number of hospital admissions in patients without acute cardiac pathology and a total of Dfl 39.632 per 100 patients was economized in the second phase. No life-threatening cardiac complications occurred in the non-hospitalized patients.

Since the evaluation of the economical costs took place after completion of the study, only few data were available for a complete cost analysis, which forms an important limitation of the present report. The following limitations should be mentioned. First, we could not distinguish between the differences in payment depending on a patients insurance (health service coverage or private insurance).

Patients who are insured at the health service coverage have to pay a fixed cost per hospital admission day, which includes the costs of any therapeutic intervention. In contrast, patients who are privately insured have to pay the costs per hospital admission day and the costs for each therapeutic intervention independantly. Since we did not gather the number of therapeutic interventions for each patient, we restricted our cost effectiveness analysis to the costs as used for the health coverage insurance.

We included the costs of the prehospital computerized ECG devices for the calculations in the second study phase. The costs consisted of procuring the ECG device, and the special electrodes system, with additional costs associated with repairs and inflation. The total costs of all ECG devices were divided by the number of recorded ECG's, which determined the costs per ECG. In addition, training of ambulance nurses or paramedics required some costs. In our experience approximately 1-2 hours additional instructions were required for application of the ECG device.

Excluded from the cost calculations were the charges of the consultation of the general practitioner, but these costs were made in both phases of the study.

Mean length of stay in the CCU was not obtained in this study. However, a distinction in length of stay in hospital could be made for patients with acute cardiac pathology versus patients with other causes of chest pain. In the first phase, the mean lenght of stay in hospital of patients with acute cardiac pathology was 9 days, whereas the mean length of stay of patients with other causes of chest pain was 6 days. In the second study phase the mean length of stay of patients with acute cardiac pathology remained similar, but the mean length of stay of patients with other causes of chest pain decreased to 4 days. When the percentages of patients with acute cardiac pathology and related length of stay in hospital were included in the present cost effectiveness analysis, it resulted in even greater savings by initial prehospital triage. Exluded were the costs of the follow-up visit of the non-referred patients in the second study phase. These additional examinations were performed to validate the decision rule, but they are not a prerequisite to implement the decision rule in general practice.

Any discussion of the value of referring low risk patients to hospital and/or admitting them to the CCU must consider the estimated cost effectiviness of alternative approaches. This study only assessed the costs of a system in which patients outside the hospital underwent additional diagnostic screening. The merits relative with hospital based screenings can not be calculated. We conclude that prehospital triage of patients by the general practitioner is an effective approach to optimize efficient use of the Coronary Care Units. It resulted in a 12% reduction of the number of patients admitted to the Coronary Care Units without acute cardiac pathology without increased risk of emergent complications in these patients. A limited analysis of the economical costs indicated that an important investment has to be made in the initial expenses of the ECG devices, but that these costs are regained by a reduction of the number of hospital admissions.

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CHAPTER FIVE

A REVIEW OF THE FEASIBILITY, SAFETY AND EFFICACY OF PREHOSPITAL THROMBOLYSIS

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Summary

Early treatment with thrombolytic agents preserves left ventricular function and reduces mortality in patients with evolving myocardial infarction. Frequently however, there is an important time delay before thrombolytic treatment can be initiated. Substantial time gain is achieved by starting treatment before hospital admission. In this article, we describe four important studies pertained to prehospital thrombolysis. The results of these studies provide compelling evidence that prehospital treatment is feasible and safe, provided that certain prerequisites, mainly related to the identification and exclusion of patients with contra-indications for such therapy, are fulfilled.

If patients with evolving myocardial infarction can be treated one hour earlier, a reduction of approximately 15 deaths for every 1000 treated patients can be achieved.

Introduction

Patients with evolving myocardial infarction can be treated with thrombolytic agents to limit infarct size and to improve short-term and long-term prognosis.[1-6] The benefit is related to the amount of jeopardised myocardial tissue and the time interval between the onset of symptoms and initiation of treatment. Thus, early treatment is an important determinant of the prognosis after acute myocardial infarction. The greatest benefit of thrombolytic treatment is obtained in patients who receive therapy within 1 hour after the onset of symptoms.[1,2,4] However, few patients are treated early because of important time delays before therapy is administered. Part of the responsibility for treatment delays rests with the patients themselves. Only 50% of all patients seek emergency medical assistance within 30 minutes from symptom onset and many wait several hours.[7] In combination with other delays such as evaluation by the general practitioner, transportation time to the hospital and treatment delay after hospitalization, this results in a small proportion of patients who are actually treated within the first hour.[8] To minimize these time delays in patients with acute myocardial infarction, it might under certain conditions be desirable to initiate thrombolytic treatment, before admission to hospital.

In numerous studies, the feasibility, safety and efficacy of prehospital administration of thrombolytic therapy have been evaluated.[9-21] In this article we will summarize the results of the four largest and most important of such studies.

Review of studies

European Myocardial Infarction Project (EMIP)

The efficacy of prehospital treatment with thrombolytic agents was examined extensively in the European Myocardial Infarction Project (EMIP).[9] This study was performed in 163 cardiological centers in 15 European countries and Canada.

Before initiation of the study the investigators estimated that treatment would result in a 15% reduction in mortality. A sample of 10,000 patients was needed to detect such a mortality reduction with a power of 90 percent and an alpha of 0.05 (in a two-sided test). After the study had been in progress for 20 months it became clear that the required number of patients would not be recruited in the originally planned 2 year study period and the trial was terminated prematurely due to depletion of funding. A total of 2,750 patients were randomly assigned to the prehospital group who received treatment with anistreplase and 2,710 to the hospital group who received placebo prehospital, followed by anistreplase after admission. The study was double-blind. If patients received placebo before admission, anistreplase was administered in hospital and vice versa. Prehospital screening, diagnosis and designation of appropriate patients for thrombolysis was done by ambulance attendants, nurses and accompanying physicians, and included a 12-lead electrocardiogram. Indications and contra-indications for study eligibility are summarized in Table 1.

The diagnosis of myocardial infarction was confirmed in hospital in 90% of the patients (Table 2). The median amount of time gained with prehospital treatment as compared with hospital treatment was 55 minutes. Ventricular fibrillation, shock and symptomatic hypotension occurred more frequently in the prehospital group during the period before hospitalisation. However, the higher incidence of these complications before hospital admission was offset by a higher incidence in the hospital treatment group during the hospital period: as a result there was no significant difference in overall incidence of these complications between the two groups.

At 30 days, 266 (9.6%) patients had died in the prehospital group as compared to 303 (11.1%) in the hospital group. The reduction in mortality following prehospital thrombolysis was 13% (95% confidence interval -1 tot 26%, p=0.08) which was statistically not significant but consistent with the initial hypothesis. It seems reasonable that the reduction in mortality could have been demonstrated with statistical significance if the investigators had indeed succeeded in randomising the originally planned 10,000 patients in their study population.

In addition, the authors performed a meta-analysis of the data on short term mortality (within 30 days) of 5 different studies that used randomization procedures comparing strategies for prehospital and in hospital thrombolytic treatment therapy.[9,10,11,16,21] Analysis of these combined results showed a significant 17 percent reduction in overall short term mortality (95% CI, 2-29%, P= 0.03) among the patients who received prehospital thrombolytic intervention.

Table 1: Indications and contra-indications for prehospital thrombolysis

	EMIP	MITI	GREAT	REPAIR
Indications				
Chest pain > 30 min duration	x		x	x
No relief by nitroglycerin	x			x
Onset of symptoms (hours)	< 6	<6	<4	<6
Maximal age 75 years		x		x
ECG findings	x	x[1]	-	x[2]
Contra-indications				
Cardiac massage	x		x	x
Artificial respiration			x	x
Systolic blood pressure	> 200	> 180	> 200	> 200
Diastolic blood pressure	> 120	> 120		
Known bleeding disorder	x		x	x
History of cerebrovascular accident	x	x	x	x
In the previous 3 months:				
Major trauma	x	x	x	x
Surgery	x	x	x	x
Puncture				x
Hemoptoë				x
Gastroduodenal ulcer or blood loss	x		x	x
Urological bleeding				x
Pregnancy/ menstruation	x		x	x
Paresis or paralysis				x
P.T.C.A.	x			
Use of coumarins	x		x	
Previous thrombolysis			x	

[1]= with use of the Marquette computerized ECG analysis
[2]= sum of ST segment elevation of more than 1 mV, Siemens, Mortara computerized ECG analysis.

The contra-indications for prehospital thrombolysis in these studies are more strict in comparison to the contra-indications in-hospital, because there are fewer resources available to recognise and treat potential complications.

Table 2: Results of Trials Comparing Prehospital and In-hospital Thrombolytic Therapy

Study	Treatment	% MI[1]	Time gain (minutes)	30 days- Mortality		
				Prehospital group	Hospital group	Relative risk (95% CI[2])
EMIP	30 Units Anistreplase	90	55	266/2750 (9.7%)	303/2719 (11.1%)	0.87 (0.74-1.01)
MITI	100 mg Alteplase, 325 mg aspirin	98	33	10/175 (5.7%)	15/185 (8.1%)	0.69 (0.30-1.57)
GREAT	30 Units Anistreplase	78	130	13/163 (8.0%)	23/148 (15.5%)	0.56 (0.25-1.23)
REPAIR	100 mg Alteplase or 1.5* 10^6 Units streptokinase	98	47	17/529 (3.0%)	34/220 (15.5%)	-
Total				306/3617 (8.5%)	375/3272 (11.5%)	

[1] Percentage final myocardial infarction during hospital admission
[2] CI denotes confidence interval

Myocardial Infarction Triage and Intervention Trial (MITI)

In the Myocardial Infarction Triage and Intervention Trial (MITI), performed in Seattle, Washington, USA, all patients with chest pain were evaluated by the prehospital care teams for possible inclusion, using a checklist with indications and contra-indications for thrombolyic therapy (Table 1).[10] In all patients, a 12-lead electrocardiogram was obtained, using a special battery powered computer-interpreted ECG (Marquette Electronics). Subsequently, the electrocardiogram was transmitted to a hospital receiver. A physician in the hospital made the final decision to randomize a patient. A total of 360 patients were identified for randomization of treatment with 100 mg alteplase (r-TPA) combined with 325 mg of aspirin before hospital admission or in hospital.

Evidence of acute myocardial infarction, as determined by serial enzyme tests and ECG's, was present in 353 (98%) of the 360 enrolled patients. When prehospital announcement of the patient's diagnosis was provided to the receiving hospital, the normal in-hospital delay reduced significantly. Because of this marked effect on decreasing hospital treatment times, the time gain achieved with prehospital administration of thrombolytic agents was only 33 minutes. There were no significant differences between the two groups with respect to 30 days mortality (5.7% in the prehospital group versus 8.1% in the hospital group) or left ventricular function (ejection-fraction of 53% in the prehospital group and 54% in the hospital group). Subanalysis showed that treatment initiated within 70 minutes of symptom onset was associated with better outcome than later treatment (mortality 1.2% vs 8.7%, infarct size 4.9% vs 11.2%, ejection fraction 53% vs 49%).

Grampion Region Early Anistreplase Trial (GREAT-study)

In de Grampion Region Early Anistreplase Trial (GREAT-study) in Scotland, the feasibility, safety and efficacy of domiciliary thrombolysis by the general practitioner was studied.[11] Entry to the study was based on strong clinical suspicion of acute myocardial infarction by the general practitioner (Table 1). The general practitioner was required to record an electrocardiogram, although no strict ECG criteria were applied for study entry. The patients were treated with thrombolytics (anistreplase) or placebo and transferred to hospital. The study was randomized and double-blind: if patients were treated with placebo before hospitalization, anistreplase was administered in hospital and vice versa.

In 78% of the patients the diagnosis of myocardial infarction was confirmed in hospital. Thrombolytic treatment could be initiated within two hours of the onset of symptoms in 189 (61%) of the patients in the prehospital group, versus only in 0.6% in the hospital group. The time gained by domiciliary administration of thrombolytic agents in this Scottish rural area amounted to 2 hours. The time saving by domiciliary thrombolysis resulted in a 49% reduction of the 3 month mortality (8% in the prehospital group vs 16% in the hospital group, p=0.04), with fewer Q-wave infarcts (p=0.02) and better left ventricular function in the survivors. Benefits were most marked with initiation of treatment within two hours after the onset of

symptoms.

REPerfusion in Acute Infarction Rotterdam (REPAIR-study)
The REPAIR-study (REPerfusion in Acute Infarction Rotterdam) was designed to evaluate the feasibility of initiation of thrombolytic treatment in patients with evolving myocardial infarction before hospital admission.[12-14] The general practitioner who requested hospital admission, or the ambulance-nurse, verified patient eligibility using a short checklist with indications and contra-indications for thrombolytic treatment (Table 1). A small portable ECG system (Sicard P, Siemens) with a diagnostic computer program was used for analysis and storage of the ECG. The ECG electrodes were mounted on a rubber mat, with extremity electrodes positioned at the shoulders and abdomen to ensure rapid placement of the electrodes. With this equipment it was possible to obtain an ECG analysis within a few minutes. Subsequently, the patient was treated with r-TPA or streptokinase and transferred to hospital. Since the initiation of the study in 1988, 248 patients were treated with 100 mg alteplase, 88 patients with 50 mg alteplase in the ambulance followed by streptokinase in hospital, and 193 patients exclusively with streptokinase. To estimate the time gained by prehospital treatment, the patients were compared to a control group of patients transferred to hospital, not eligible for prehospital thrombolysis at that moment, but who received thrombolytic treatment as soon as possible after clinical evaluation in hospital. This control group consisted of 220 patients.

In 98% of the 529 patients treated with prehospital thrombolytics (alteplase and/or streptokinase) since 1988, the diagnosis myocardial infarction was confirmed in hospital. Thrombolytic therapy in the prehospital study population was initiated within an average of 20 minutes after arrival of the ambulance. Average time to administration of alteplase in the control group after arrival of the ambulance was 69.0 $\pm$ 26 minutes. The average time gained with prehospital treatment was thus 49 minutes (95% confidence interval, 47 - 52). In the prehospital group, 28% of the patients were treated within 1 hour after symptom onset, compared to only 1% in the control group. Four patients died before thrombolytic treatment could be started. The number of complications during transportation to the hospital was low in both the group who was treated with alteplase as in the group who received streptokinase, although symptomatic hypotension and allergic reactions were observed more in patients treated with streptokinase (Table 3). The prognosis of the patients was excellent. Only 2% of the patients in the prehospital group died during the first 24 hours.

Table 3: Complications in the prehospital period and during hospitalisation in the first 24 hours (REPAIR)

	Prehospital	In Hospital	Total (%)
Mortality	5	12	17 (3.0%)
Ventricular fibrillation	14	27	41 (7.8%)
CPR[1]	4	15	19 (3.6%)
Major bleeds	-	18	18 (3.4%)
Hypotension	-	33	33 (6.3%)
Allergic reaction	4	8	12 (2.3%)

[1] denotes cardiac pulmonary resuscitation

Discussion

Previous studies of timely thrombolytic therapy have shown significant reductions in mortality, limitation of infarct size, and improvement in left ventricular function.[1-6] Significant time gain has been documented by initiation of thrombolytic therapy before hospital admission.[9-21] This time gain varied from 33-130 minutes.[9-14] The percentage of patients who received thrombolytic therapy within the first hour of symptom onset increased from 1% in the hospital group to 28% in the prehospital group in the REPAIR study.[12,14] Similarly, in the MITI trial, thrombolytic treatment was initiated within the first hour of symptom onset in 33% of the patients compared to only 4% of the hospital- allocated group. In the GREAT study, 12% of the patients received thrombolytic treatment within 1 hour of the onset of symptoms and 61% within 2 hours. This is of major importance, because the greatest benefits are observed in patients treated within the first 60-90 minutes after symptom onset.[1-4] Relative to the in-hospital treatment, prehospital thrombolytic intervention resulted in a 17% lower mortality at 30 days ($P< 0.05$) as determined in the meta-analysis of 5 studies by the EMIP study group.

Most patients do not achieve maximum therapeutic benefit because of delays in administration of the therapy. The largest delay usually occurs in the period during which a patient decides to summum medical assistance.[8] Subsequently, it is sometimes difficult for the general practitioner to establish the correct diagnosis immediately.[7] Media campaigns initiated to affirm the attention of the patient to early recognition of symptoms of myocardial infarction resulted only in a temporarily decrease in the time delay before medical assistance was sought.[22] In hospital, treatment is often delayed due to many administrative and diagnostic procedures, exclusion of contra-indications and the time in which a resident has to consult the supervisor in order to initiate thrombolytic treatment. In-hospital delays vary from 30-90 minutes in most hospitals.[17,19] In the Netherlands, the in-hospital delays were

determined in 17 hospitals.[23] The results of this analysis showed a median in-hospital delay of 35 minutes, which is surprisingly low in comparison to previous studies. In total, 50% of the time gained by prehospital thrombolysis is due to avoidance of the in-hospital delay. The prehospital procedure for selection and treatment is considerably faster than similar procedures in hospital. In addition, the use of a computerized analysis of an ECG made "on the spot" as used in the MITI and REPAIR trials provided a more rapid ECG interpretation as compared with the ECG interpretation in hospital and this attributed also to a reduction in the treatment delay time.

A large number of studies in different settings confirmed that evaluation of potential candidates for prehospital thrombolysis can be performed efficiently either by physicians accompanying ambulance teams,[9] by a general practitioner,[11-14] but also by ambulance- nurses,[12-14] or other ambulance personnel.[10] In the REPAIR study, competent organization of the ambulance service, skilled ambulance-nurses and good cooperation with the general practitioners were of major importance for the success of the study. Even before initiation of the REPAIR project, the level of education of the ambulancenurses was high. All completed a full 6 years education in basic somatic and psychiatric nursing, with advanced education in Coronary Care and Intensive Care. At 2-years intervals sessions of practical training in emergency medicine are followed, with emphasis on cardiac resuscitation, endotracheal intubation and insertion of intravenous lines. The most common arrhythmias can be recognized and treated. Instructions for establishing patients eligibility and initiation of thrombolytic treatment did not require much additional education time: about one hour per person.

The safety of prehospital treatment in the REPAIR study was guaranteed by strict selection of eligible patients. Patients at increased risk of bleeding (in particular intracranial hemorrhage) were excluded and treatment was limited to patients with extensive evolving myocardial infarction. On purpose, more strict indications for thrombolytic therapy were applied in the REPAIR study in comparison to the indications for such treatment in- hospital. In the EMIP study, eligibility was established based on a patient's history and analysis of a 12-lead ECG without strict ECG criteria. Randomisation was stratified according to presence or absence of ST segment elevation. Strict criteria were used in the MITI trial. A physician in the hospital reviewed the findings (both clinical and ECG) from the mobile emergency unit over the telephone and made the final decision to include a patient. In the GREAT study, study entry was based on strong suspicion of myocardial infarction by the general practitioner, without strict ECG criteria. The percentage of confirmed myocardial infarction in hospital in that study was lower; 78%, in comparison to the other studies.

Life-threatening complications during transportation time to hospital were rare. In the REPAIR study 4 patients died before thrombolytic therapy was initiated. One patient died during transportation. No major bleedings occurred. Ventricular fibrillation occured in 14 out of 529 patients and was successfully treated in all

patients. In the EMIP study, 6.2% of the patients in the prehospital group developed ventricular fibrillation versus 7.0% in the hospital group. Complications during the hospital period in the prehospital treated patients did not differ from the complications in the hospital treated group.

The financial costs in the REPAIR study were limited to the additional equipment of the ambulances with a computerized ECG device, a battery powered infusion pump, the education of the ambulance-nurses (1 hour per person) and the salary of the physician who accompanied the study during the first years.

It is concluded that prehospital thrombolytic therapy in patients with evolving myocardial infarction is feasible, effective and safe. Accurate identification of patients with a myocardial infarction is of major importance. Still, immediate recognition of acute myocardial infarction in patients with chest pain is often difficult. In the Netherlands most patients are seen primarily by their general practitioner. The clinical information available for the general practitioner is often insensitive or nonspecific. The I.M.I.R. investigators found a sensitivity of only 44% for the diagnosis "myocardial infarction" by the general practitioner, based on information from history and physical examination.[24-26] The sensitivity increased to 59% after adding the findings from an electrocardiogram. The presence of an electrocardiogram recorded 'on the spot' is therefore fundamental. However, procuring an ECG device is not a priority for the general practitioner. Moreover, it will be difficult for the general practitioner to maintain the required skills of ECG interpretation at a low incidence of myocardial infarction patients in their practice. This problem was avoided in the REPAIR study by the implemention of a computerized ECG device in the ambulance.

The obtained time gain with prehospital initiation of thrombolytic therapy results in a significant reduction of mortality: if patients with evolving myocardial infarction can be treated one hour earlier, it will lead to a reduction of 15 deaths in every 1000 treated patients! Consequently, prehospital thrombolytic treatment can be encouraged, provided that the diagnosis of myocardial infarction can be made with certainty and that patients with a high risk of complications are excluded.

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CHAPTER SIX

PREHOSPITAL THROMBOLYTIC THERAPY WITH EITHER ALTEPLASE OR STREPTOKINASE; PRACTICAL APPLICATION, COMPLICATIONS AND LONG-TERM RESULTS IN 529 PATIENTS

Key words: myocardial infarction, thrombolysis, long-term results.

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Abstract

Objective- To assess the practical application, safety and long term outcome of prehospital thrombolytic intervention with either alteplase or streptokinase in patients with extensive myocardial infarction.
Design- Prospective study.
Subjects- Patients with chest pain of more than 30 minutes duration, presenting within 6 hours after symptom onset and with electrocardiographic evidence of extensive evolving myocardial infarction.
Methods- Eligibility of patients was established by the general practitioner or the ambulance nurse using a standardized questionnaire with (contra-) indications for thrombolytic therapy. Computerized ECG was recorded by ambulance nurses. In the presence of ST-segment elevation (sum ST deviation $\geq$ 1.0 mV), eligible patients received either 100 mg alteplase (N= 246) or 50 mg alteplase in the ambulance followed by $0.75*10^6$ IE streptokinase in hospital (N= 90), or $1.5*10^6$ IE streptokinase intravenously (N= 193).
Main outcome measurements- Death and life-threatening complications (ventricular fibrillation, cardiac arrest) and side effects (hypotension, allergic reactions) during transportation to hospital and in the first 24 hours following hospitalization, and survival up to 5 years follow-up.
Results- From 1988-1993, 533 patients were eligible for prehospital thrombolytic treatment. 4 patients died before receiving thrombolysis. A total of 529 patients received prehospital initiated thrombolytic treatment. Mean time gained by prehospital administration of thrombolysis was 47 minutes. The rate of complications during transportation and during the first 24 hours after hospitalization was low. Hospital mortality was 2% and 1-year mortality 3%. The cumulative survival rate at five years follow up was 92% and was similar among the different thrombolytic treatment regimens. This was superior to the 84% 5 year survival rate observed in another group of 239 patients treated with alteplase in hospital with similar baseline characteristics.
Conclusions- Prehospital administration of either alteplase or streptokinase is feasible and safe and results in significant time gain. The long term prognosis is excellent in spite of extensive evolving myocardial infarction upon admission.

Introduction

The value of thrombolytic therapy in patients with evolving myocardial infarction is well documented. Still, the gain in survival by thrombolytic therapy diminishes if such therapy is started later after the onset of symptoms. The earlier thrombolytic therapy is initiated, the greater the benefits.[1-6] In clinical practice, only a small minority of patients receives treatment within the first hour after onset of symptoms. Many patients wait several hours before alerting the general practitioner or the ambulance service and it takes additional time for the general practitioner to respond and

establish the diagnosis.[7-9] Ambulance transport and in- hospital delivery of thrombolytic therapy also carry inherent delays.[10]

Efficient strategies have been developed to ensure rapid prehospital initiation of thrombolytic therapy.[11-24] In the Netherlands, the REPAIR-study (REPerfusion in Acute Infarction Rotterdam) was designed to evaluate the feasibility of prehospital thrombolytic intervention by general practitioners and ambulance nurses.[11,13,18] Here, we report the practical application and complications associated with prehospital thrombolytic therapy with either alteplase or streptokinase in 529 patients during the 5 year period of the REPAIR study. The long term outcome of prehospitally treated patients compared with the outcome of another group of patients with similar baseline characteristics treated in hospital, is reported.

Patients and methods

The REPAIR study was initiated in June, 1988. After extensive field testing, prehospital thrombolytic treatment was accepted as routine management in the Rotterdam Ambulance Service in January, 1991. The indications for prehospital initiation of thrombolytic therapy have been described previously.[11,13,18] In short, the referring general practioner, or in his/her absence the ambulance nurse, checked the criteria for eligibility in all patients with chest pain suggestive of myocardial infarction using a short questionnaire (Table 1). These selection criteria were more restricted than those used in the hospitals to minimize the risk of inappropriate selection of patients for thrombolytic therapy or inclusion of patients at high risk of bleeding. A small portable ECG system (Sicard P, Siemens, Sweden) with special easy application electrodes and a diagnostic computer program (Mortara Inc, Milwaukee, USA) was used to confirm the presence of an evolving myocardial infarction with extensive myocardial ischemia (defined as a summed ST segment deviation of more than 1.0 mV in the absence of bundle branch block, and QRS complex wider than 130 msec).[13,18]

All patients received basic medical care, provided by the general practioner or the ambulance nurse, including oxygen, nitrates, and rhythm monitoring. Eligible patients were subsequently treated with alteplase or streptokinase intravenously, before they were transferred to hospital. Until 1991, patients received 100 mg alteplase. For economical reasons, this treatment was replaced by 1,500,000 Units of streptokinase. In the meantime, a group of patients received alteplase prior to hospital admission (one vial of 50 mg), followed by 750,000 IE of streptokinase in hospital.

Complications and side-effects were recorded during transportation in the ambulance as well as in the first 24 hours following hospitalization. Long term outcome was determined using information from the hospital and from the municipal registries. Four patients died before treatment could be initiated and they were excluded from the study.

Table 1

Indications for prehospital thrombolytic therapy (REPAIR)
Chest pain of more than 30 minutes duration
No relief by nitroglycerin
Onset of symptoms < 6 hours
Age ≤ 75 years
ECG: sum ST elevation ≥ 1.0 mV in the absence of bundle branch block, QRS complex wider than 130 msec[1]
Contra-indications for prehospital thrombolytic therapy (REPAIR)
Cardiac massage
Artificial respiration
Systolic blood pressure > 200 mm Hg
Known bleeding disorder
History of cerebrovascular accident
In the previous 3 months:
Major trauma
Surgery
Hemoptoe
Gastroduodenal ulcer or blood loss
Urological bleeding
Pregnancy / menstruation
Paresis or paralysis
Previous thrombolysis

[1] More detailed description of ECG algorhythm in previous publications. Patient selection for prehospital therapy was more strict than in hospital to allow for the limited time available for assessment and for limited experience of general practitioners and ambulance nurses.[11,13,18]

In order to compare the time to treatment and the long term outcome two non-randomized control groups were selected. To estimate the time gained by prehospital administration of thrombolytic therapy, treated patients were compared to a control group of patients transferred to hospital, who were not eligible for prehospital thrombolysis at that moment, but who received thrombolytic treatment immediately after clinical evaluation in hospital.[13,18] Long term survival in REPAIR was compared with survival in patients treated in hospital. To obtain such control group, 491 patients were selected from a data base of a previous study with alteplase,[26] using the same selection criteria as applied in REPAIR.

Group differences were assessed with Student-t, ANOVA, and chi-square tests for continuous or dichotomous variables, respectively. Two tailed p-values <0.05 were considered statistically significant. Survival curves were generated using the Kaplan-Meier method.

Results

Between June 1988 and June 1994, 529 patients received prehospital thrombolytic therapy: 246 patients were treated with alteplase only, 90 patients with alteplase in the ambulance followed by streptokinase in hospital, and 193 patients with streptokinase. Baseline characteristics of these patients are shown in Table 2.

Table 2: Characteristics of patients treated with thrombolytic agents before hospitalization during 6 consecutive years.

	1988[1]	1989	1990	1991	1992	1993[2]
Total number	36	65	126	116	103	83
Male gender	32 (89)	62 (95)	105 (83)	98 (84)	79 (77)	64 (77)*
Mean age (yrs)	59.3	56.7	57.7	59.4	60.9	60.4*
Treatment with alteplase	36 (100)	65 (100)	120 (95)	21 (18)	2 (2)	-
Treatment with SK	-	-	6 (5)	95 (82)	101 (98)	83 (100)
Anterior infarction	11 (30)	25 (38)	48 (38)	41 (35)	35 (34)	25 (30)
Infusion in ambulance	32 (89)	63 (97)	124 (98)	114 (98)	101 (98)	83 (100)
False positive ECG	1 (3)	3 (5)	-	2	1 (1)	-
Treated < 1 hour	7 (19)	12 (18)	36 (29)	29 (25)	32 (31)	33 (40)*

* $P < 0.05$
[1] Second half 1988 only
[2] First half 1993 only
Percentages between parentheses.

Patients were younger, and more frequently male during the first three years in comparison to the group, treated after 1991. This was caused by extension of the age limit from 70 during the initial program to 75 years from 1991 onward. In the initial phase of the study, 11% of the intravenous lines could not be inserted in the ambulance. This decreased significantly in the course of the study as a result of increased experience of the ambulance nurses. During the 5 year study period, 7 patients without myocardial infarction were erroneously included (false positive rate 1%) as a result of noisy electrocardiographic signals, resulting in a false positive computer interpretation. One patient was treated based upon a previous electrocardiogram, recalled from the computer memory.

Prehospital complications were rare (Table 3). Ventricular fibrillation occurred in 2% and was successfully treated by defibrillation in all patients. There were no bleedings or deaths outside hospital, although CPR was necessary in 1%. During the first 24 hours after hospitalization, 2% of the patients died. No significant differences were observed between the thrombolytic agents, although symptomatic hypotension and allergic reactions occurred more often in patients treated with streptokinase. The main source of minor bleeding was the intravenous access site. Only 2% of the patients required blood transfusions.

Overall, 5% of the patients received additional thrombolytic therapy for recurrent infarction in hospital.

Table 3: Complications prehospital and in the first 24 hours after hospitalization.

Complications	r-TPA[1] N=246	r-TPA, SK[2] N=90	SK[3] N=193	Total N=529
PREHOSPITAL				
Mortality	-	-	-	-
Ventricular tachycardia	-	-	1 (1)	1 (1)
CPR/ Ventricular Fibrillation[4]	8 (3)	3 (3)	5 (2)	16 (3)
Hypotension	-	-	2 (1)	2 (1)
Allergic reaction	-	-	2 (1)	2 (1)
IN HOSPITAL				
Mortality	4 (2)	1 (1)	5 (3)	10 (2)
Ventricular tachycardia	23 (9)	6 (7)	5 (3)	34 (6)
CPR/ Ventricular fibrillation	26 (11)	8 (9)	21 (11)	55 (10)
Hypotension	4 (2)	3 (3)	23 (12)	30 (6)
Allergic reaction	-	-	3 (2)	3 (1)
Major bleeding[5]	8 (3)	1 (1)	3 (2)	12 (2)
Minor bleeding	29 (12)	7 (8)	27 (14)	63 (12)
Additional thrombolytics	9 (4)	4 (4)	12 (6)	25 (5)

[1] 100 mg alteplase

[2] 50 mg alteplase in the ambulance, followed by $0.75*10^6$ IE streptokinase in hospital

[3] $1.5*10^6$ IE streptokinase

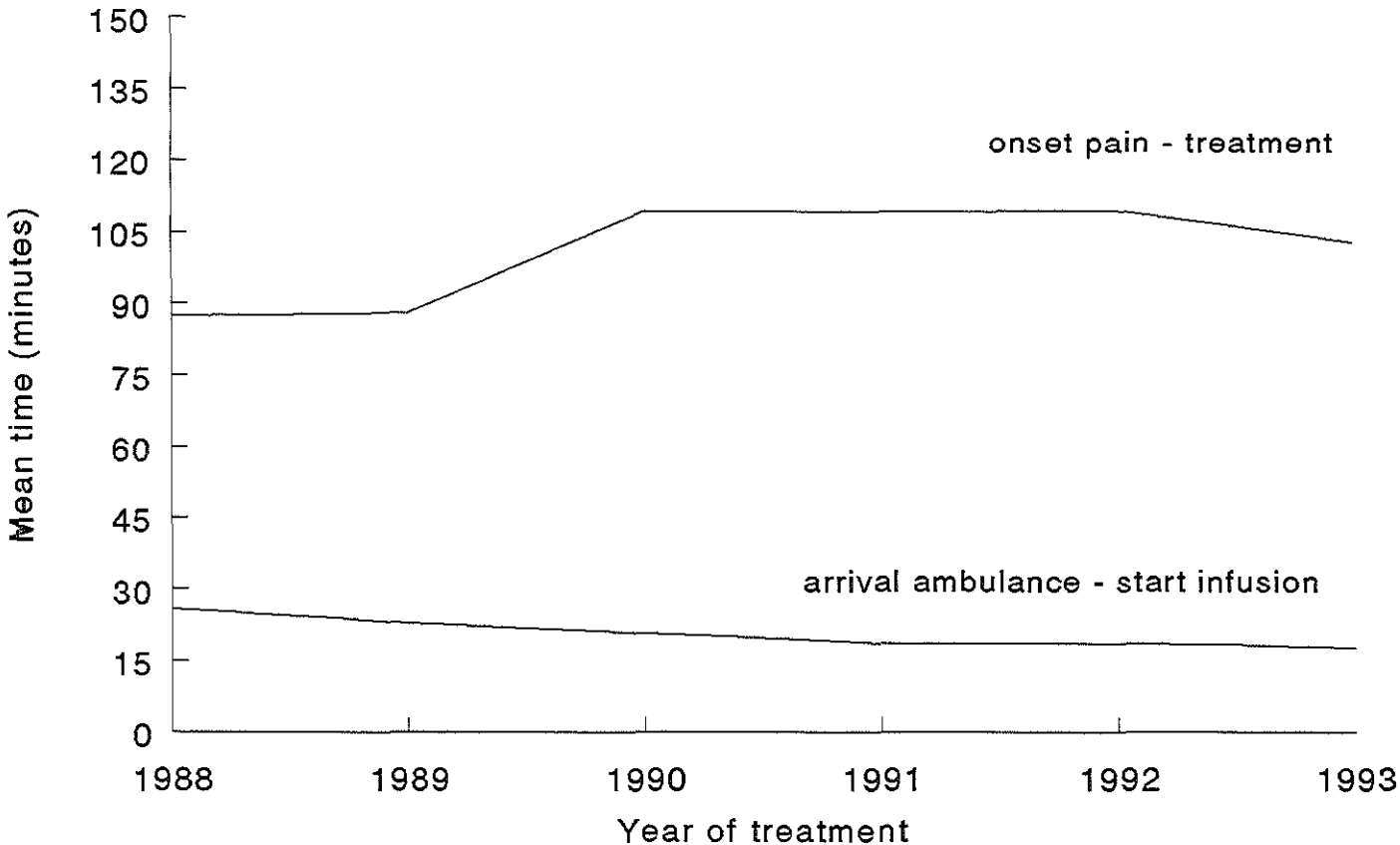
[4] CPR= Cardiac Pulmonary Resuscitation

[5] Cerebrovascular accidents or severe bleedings requiring blood transfusion.

Delay- time gained: The mean delay between onset of symptoms and ambulance call was 75 ± 67 minutes. In the initial phase of the study, this delay was shorter (mean 55 ±39 minutes), because the time window at that time for therapy was 4 hours, which was subsequently increased to 6 hours. After arrival of the ambulance, 22 ± 9 minutes elapsed for evaluation of patient eligibility until initiation of thrombolytic treatment. This interval gradually shortened in the course of the project (Figure 1).

Average time to administration of thrombolytic agents in the control group was 69 ± 26 minutes after arrival of the ambulance. This group consisted of 220 patients, treated in 1988. In this control group, 75% were men, the mean age was 60 years and 47% had anterior myocardial infarction. Since thrombolytic therapy in the prehospital study population was initiated within an average of 22 minutes after arrival of the ambulance, the mean time gained with prehospital treatment was 47 minutes (95% confidence interval, 44 - 51). Initially, 19% of the patients were treated within the first hour after the onset of symptoms which increased to 40%. In contrast, only 1% had thrombolytic treatment initiated within

Figure 1: Total time between the onset of symptoms and initiation of prehospital thrombolytic treatment and the time elapsed between arrival of the ambulance and start of infusion during 6 consecutive years.



the first hour after the onset of symptoms in the control group.
Long term outcome: Kaplan-Meier survival curves of patients who received alteplase, combined treatment, and streptokinase are shown in Figure 2. The mean follow-up time was 3.0 years. The long term outcome was excellent. The cumulative survival was 97% at one year and 92% at five years: 89% in the streptokinase group, 91% in the alteplase and streptokinase group and 97% in the alteplase group. These differences were not statistically significant. For comparison a subgroup of patients was selected from a previous trial, with similar inclusion criteria as in REPAIR.[26] Out of 721 patients in that study, 491 had ECG evidence of extensive evolving myocardial infarction with a sum of ST elevation $\geq$ 1.0 mV. In this series treatment was initiated approximately 3 hours after symptom onset. Other patient characteristics were similar to REPAIR (Table 4). 239 patients had been treated with alteplase and 252 received placebo. At 1 year mortality was 3% in REPAIR, 6% in patients receiving alteplase in hospital and 12% in the hospital placebo group. At five years these figures were 8%, 16%, and 18% respectively. These prehospital observations support the concept that very early thrombolytic therapy as achieved in REPAIR is associated with better outcome than in hospital treatment.

Table 4: Comparison of patients treated with thrombolytic therapy in the REPAIR study and ECSG study

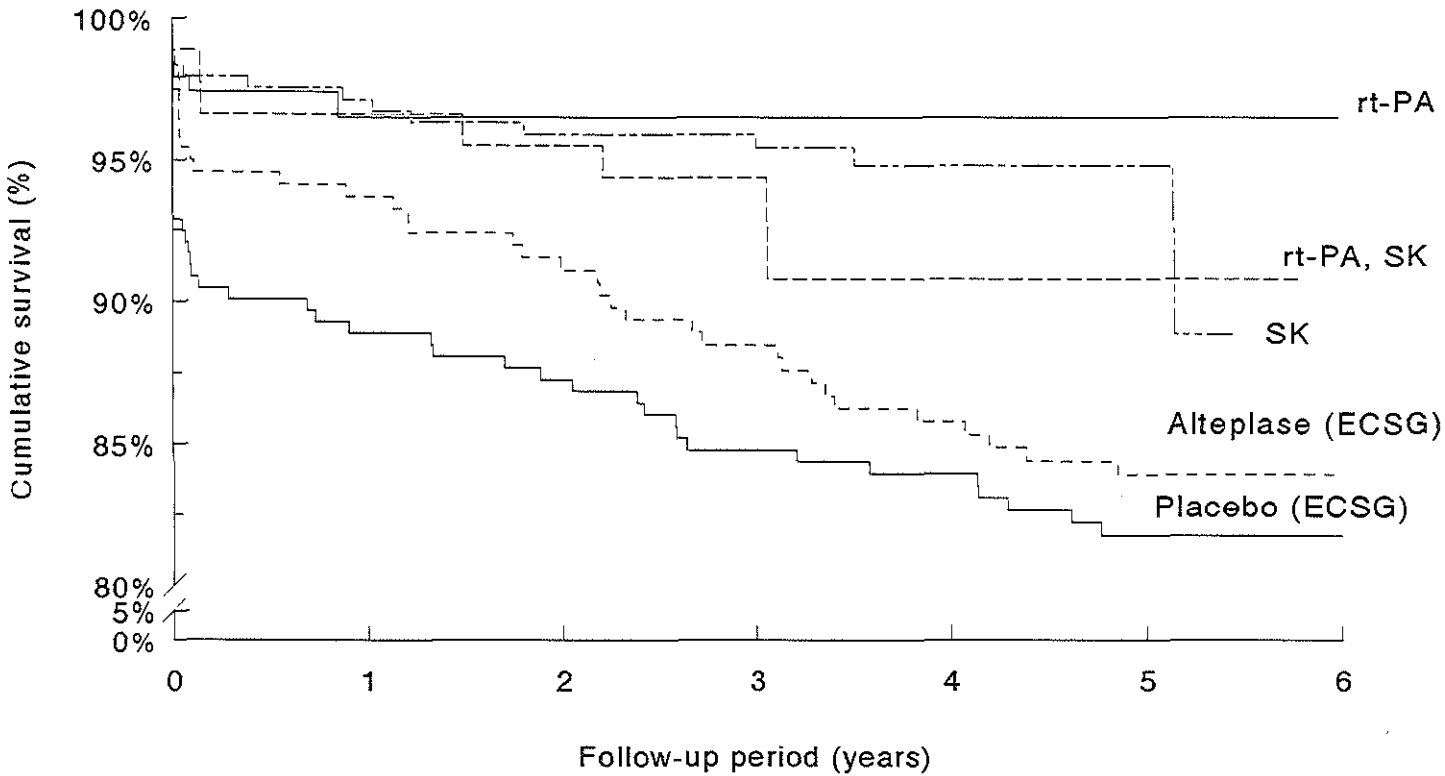
	REPAIR[11,13,18]	ECSG*	
	Total	r-TPA	Placebo
Number of patients	529	239	252
Male gender (%)	440 (83)	211 (88)	210 (83)
Mean age	59.1	57.0	57.2
Time to treatment (minutes)	104	175	170
% Treated < 2 hours	393 (74%)	44 (18)	50 (21)
Mortality			
Hospital (%)	98	99	91
1 Year (%)	97	94	88
5 Years (%)	92	84	82

* Patients from the European Cooperative Study Group with a total summed ST segment of $\geq$ 1.0 mV.

Discussion:

Feasibility: The REPAIR experience since 1988 confirms that identification of candidates for thrombolytic therapy in the prehospital setting is feasible. Prehospital therapy with either alteplase or streptokinase appeared to be safe and resulted in a significant time gain when compared to in-hospital therapy after ambulance transport. An unique feature of the REPAIR program is the initiation

Figure 2: Kaplan-Meier survival curves comparing patients who received alteplase, alteplase, streptokinase, and streptokinase before hospital admission in the REPAIR study, and in patients who received alteplase or placebo in the ECSG study.



of therapy by experienced ambulance nurses, even when no physician (general practitioner) is present. Competent organization of the ambulance service, skilled ambulance-nurses and good cooperation with the general practitioners were of major importance for the success of the study. Even before initiation of the REPAIR project the level of education of the ambulance-nurses was high. All completed 6 years education in basic somatic and psychiatric nursing, with advanced education in Coronary Care and Intensive Care. The diagnosis of myocardial infarction was confirmed in hospital in 98% of the patients, who received prehospital thrombolytic intervention. The false positive rate was low, and appeared related to technical problems, which have been resolved since.

The MITI project in Seattle was also conducted by ambulance paramedics using telephone transmission of the ECG for immediate review and interpretation by a physician.[23] All other prehospital programs were conducted by physicians in the ambulances using standard electrocardiography.[14-17,20-24] In many communities, however, ambulances are manned by paramedics in stead of physicians. The combined REPAIR and MITI experience have confirmed that thrombolytic therapy can be given safely and effectively in such setting.

Time gain and outcome: The time gain by prehospital thrombolytic therapy in Rotterdam was 47 minutes. At the early phase of the program an average of 26 minutes elapsed between arrival of the ambulance and initiation of thrombolytic therapy. This time decreased significantly to 17 minutes in 1993, as a result of improved routine of the ambulance nurses. In other series the time gain by prehospital therapy ranged from 33- 130 minutes.[14-20]

In REPAIR 28% of patients were treated within 2 hours after symptom onset. Such early therapy resulted in very low mortality figures in spite of prehospital selection of patients with ECG evidence of large evolving myocardial infarction. One year survival was 97%, and 5 years survival was 92%. Such excellent survival figures have not been reported from any other series of patients treated in hospital. This supports the concept that very early thrombolytic therapy is indeed life saving, even though no randomized control group is available in our series. In a non-randomized but otherwise comparable group of patients treated in hospital, 5 years survival was 84%. The EMIP study was a randomized comparison of prehospital and in-hospital therapy. Treatment in EMIP was initiated approximately half an hour later, averaging 130 and 190 minutes after onset of symptoms respectively. Still, hospital mortality was reduced by prehospital therapy to 9.7% compared with 11.1% for hospital therapy (95% CI -1-26%, P=0.08). A combined analysis of all randomized trials comparing prehospital and in-hospital therapy yielded a significant 17% reduction of mortality (95% CI, 2-29%, P= 0.03). The additional value of very early therapy was also shown in an analysis of the MITI study, where mortality was only 1.2% in patients treated within 70 minutes of symptom onset and 8.7% in those treated later (P= 0.04). A recent meta-analysis of large randomized trials reported a loss of benefit of thrombolytic therapy of 1.6 ± 0.6 per 1000 for an additional delay of

1 hour, or an additional benefit of 1.6 per 1000 for earlier therapy by 1 hour.[6] The benefit of prehospital therapy in EMIP and other randomized trials was almost ten fold higher: 14 per 1000 patients! Together with MITI and the very low mortality in REPAIR thus supports the concept that prehospital therapy is effective, particularly if a large proportion of patients can be treated within one or two hours. It should be appreciated that most patients in these trials were treated more than 2 hours after the onset of symptoms. Furthermore, patients were not randomized to receive earlier or later therapy, thus characteristics of patients treated at different intervals were probably not the same.

Cost effectiveness of prehospital thrombolytic therapy: There is no doubt that prehospital thrombolytic therapy should be a preferred mode of treatment, provided that a cost effective system can be established. Both the additional costs and the effectiveness of systems for prehospital thrombolytic therapy will depend on the setting in which a system is introduced. The benefit will be greater if patients can be reached very early[11,13,16,18], and in settings where transportation time is long[19]. In other environments, intermediate benefit will be achieved such as those participating in the large multicentre EMIP study. Electrocardiography is required to establish a diagnosis of evolving myocardial infarction with sufficient certainty to initiate thrombolytic therapy. Thus an electrocardiograph must be added to the ambulance equipment. Currently computer ECG systems such as used in REPAIR can be obtained at acceptable low prices, in the range of Dfl 10,000 - 15,000. Furthermore integrated systems, designed especially for the ambulance environment, are available and being developed which include in a single portable unit: a defibrillator, ECG monitor (1-2 channels), a diagnostic 12-lead ECG recorder and other related features. Costs will increase if telephone transmission of the ECG is required for physician review and time gain will diminish.[16] However, the REPAIR experience indicated that such review is not necessary, while it would also cause additional delay since transmission is not always reliable, and since the physician at the central receiving station may be occupied by other tasks.

Additional training of ambulance nurses or paramedics will require some costs, depending on the level of expertice which is present. A first requirement for ambulance personnel is basic life support including interpretation of arrhythmias, using an ECG monitoring and intravenous drug administration. In our experience approximately one hour additional training was required to initiate prehospital thrombolytic therapy, with subsequent feed-back and discussion of the cases encountered in practice. The additional costs for the program for prehospital therapy in Rotterdam were estimated to be Dfl 70,000 - Dfl 100,000 per year, which makes it a cost effective program.

Conclusion: In the prehospital setting, patients with a large evolving myocardial infarction can be identified with a simple questionnaire and a computerized portable ECG system. In such patients immediate thrombolytic therapy with either alteplase or steptokinase is feasible and safe, and results in excellent in-hospital

and long term survival. The establishment of similar systems in other environments should be encouraged.

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CHAPTER SEVEN

A COMPARISON BETWEEN HOME- AND HOSPITAL- DERIVED ECG'S IN PATIENTS WITH CHEST DISCOMFORT.

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Introduction

In patients with possible evolving cardiac pathology both the history, physical examination and the electrocardiogram provide important information for diagnosis and initial patient management. Accordingly, a system was developed for prehospital triage in Rotterdam, combining a systematic standardized questionnaire (history and limited physical examination) and computerized interpretation of the ECG. Through the triage, three groups of patients were identified: (1) those with extensive evolving myocardial infarction to receive prehospital thrombolytic therapy;[1-4] (2) an intermediate group which required hospital admission for further evaluation and (3) patients at low probability of acute cardiac pathology (stable angina pectoris, atypical chest pain) in whom hospitalization might be avoided.[5,6]

To allow rapid recording and analysis of a 12-lead ECG, a modified system for electrode placement was used, with a dedicated portable computer ECG system.[7] In this manuscript we compare prehospital ECG recordings with the modified lead placement with standard hospital ECG recordings in 126 patients. The purpose of this analysis was to verify the reliability of the prehospital recording system.

Methods

The study population included all patients consecutively admitted to the University Hospital of Rotterdam from January 1, 1992 through April 1, 1994. Eligible were all patients with chest discomfort of possible cardiac origin, who according to the general practitioner, necessitated further cardiological evaluation in-hospital, and in whom after arrival of the ambulance, a 12-lead ECG was recorded with a small portable battery-powered computer ECG device (Sicard-P, Siemens, Sweden). The ECG electrodes were mounted on a rubber mat, with extremity electrodes positioned at the shoulders and abdomen to ensure rapid placement of the electrodes. The 12-lead ECG was analysed by a computer-program, developed by Mortara, and stored for later analysis.[7] After arrival of the patients in the emergency room of the hospital, an additional standard 12-lead ECG was recorded with use of the Hewlett-Packard electrocardiograph.

Classification of electrocardiograms- The prehospital ECG findings were recoded as shown in Table 1. If more than one finding was present, the most severe ECG finding was chosen. The ECG's recorded in the hospital were interpreted and coded similar to the prehospital ECG's without knowledge of the previously recorded prehospital ECG or the subsequent in- hospital course.

Data analysis- Chi-square analysis was used to compare the presence of electrocardiographic findings of the prehospital and hospital derived ECG's. P values < 0.05 were considered significant.

Results

The mean age of the 126 patients in this analysis was 44.5 years (median 38.0 years, range 31.8 to 91.6); 72% was men. A final diagnosis of myocardial infarction was made in 34 patients (27%), unstable angina pectoris was present in 30 patients (24%), while 62 patients (49%) had a diagnosis of stable angina pectoris or atypical chest pain. In 61 patients (48%), the time interval between the prehospital ECG recording and the onset of symptoms was less than 3 hours. The distribution of the time interval between the prehospital ECG recording and the in-hospital ECG recording is presented in Figure 1. The mean time interval was 43 ± 38 minutes.

The number of patients with different electrocardiographic findings in the prehospital and hospital derived ECG's are shown in Table 1.

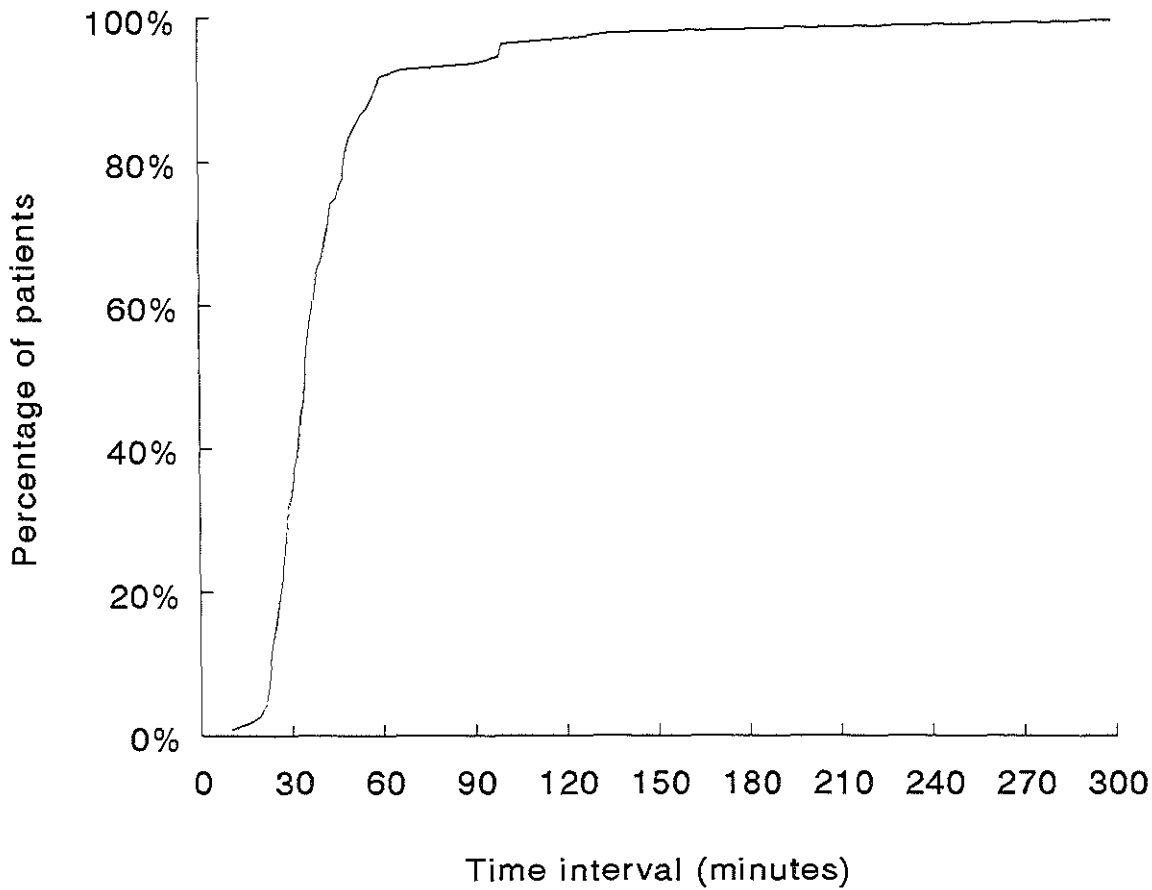
Table 1: Distribution of electrocardiographic findings recorded at home and after hospital admission

Electrocardiographic findings	Code	Home (%)	Hospital (%)
Bundle branch block	1	13 (10)	14 (10)
ST elevation[1]			
Anterior/lateral/anterolateral	2	6 (5)	6 (5)
Inferior	3	4 (3)	6 (5)
Anterior and inferior	4	-	-
ST depression without ST elevation[2]	5	25 (20)	22 (17)
Q waves[3]	6	19 (15)	17 (13)
T wave inversion[4]	7	12 (10)	12 (10)
Minor abnormality[5]	8	6 (5)	7 (6)
Other[6]	9	2 (1)	-
Normal	10	39 (31)	42 (33)
Total		126 (100)	126 (100)

[1]: ST elevation ≥ 1 mm in two limb leads or ≥ 2 mm in two precordial leads
[2]: ST depression ≥ 0.5 mm
[3]: Q wave duration ≥ 40 msec in any lead
[4]: T waves with peaking or inversion of ≥ 1 mm
[5]: ST elevation ≤ 1 mm in two limb leads or ≤ 2 mm in two precordial leads or ST segment depression < 0.50 mm
[6]: all abnormalities in the absence of bundle branch block, Q waves or ST segment deviations.

The most frequent ECG finding was ST depression in both the prehospital recorded ECG group and the hospital recorded ECG group. Isolated ST segment elevation was present in only 8% of the home ECG recordings and 10% of the hospital recordings. Rhythm findings were categorized into: sinus rhythm, supraventricular rhythm and pacemaker rhythm (Table 2). There were no patients with ventricular rhythm disturbances. In total, 113 patients (90%) had similar rhythms on their home and hospital derived ECG's. 13 patients with a supraventricular rhythm on their

Figure 1: The time elapsed between the prehospital ECG recording and the in-hospital ECG recording in 126 patients.



home recorded ECG had a sinus rhythm in the hospital.

Table 2: Electrocardiographic rhythm findings recorded at home and in hospital.

	Home electrocardiogram			
Hospital electrocardiogram	Sinus rhythm	Supraventricular rhythm	Pacemaker rhythm	Total
Sinus rhythm	97	13	-	110
Supraventricular rhythm	-	13	-	13
Pacemaker rhythm	-	-	3	3
Total	97	26	3	126

In addition, the ECG findings were classified into 3 categories: ST elevation or bundle branch block (codes 1,2,3,4), non-specific changes (codes 5,6,7,8,9) and normal ECG (code 10). In Table 3, a comparison is made between the home recorded ECG's and subsequent hospital recorded ECG's. The electrocardiographic code differed between home and hospital recording in 32 patients (25%). In total, 94 patients with symptoms suggestive of acute cardiac pathology showed no change of category. All home recorded ECG's with a bundle branch block or ST segment elevation did not undergo change. Of the 64 patients with non-specific abnormalities on their home recorded ECG's, 3 developed ST segment elevation and 16 patients had a normal ECG in hospital. If the home ECG was initially normal, 13 patients developed non-specific changes.

Table 3: Specific electrocardiographic findings recorded at home and in hospital.

	Home electrocardiogram			
Hospital electrocardiogram	ST elevation/ bundle branch block	Non-specific abnormalities	Normal ECG	Total
ST elevation/ bundle branch block	23	3	-	26
Non-specific abnormalities	-	45	13	58
Normal ECG	-	16	26	42
Total	23	64	39	126

Finally, ST segment elevations present in any lead were summed and subsequently categorized in 5 groups with increasing amount of total ST segment elevation (Table 4). This analysis demonstrated that 103 patients (82%) had similar ST segment findings on their home and hospital recorded ECG's. 10 patients (8%) with an initial normal home ECG developed ST segment elevation on their hospital ECG. In 12 patients, the total amplitude of ST segment elevation on their home ECG

was higher in comparison to the hospital ECG's, whereas in 11 patients the total amount of ST segment elevation decreased during transportation to hospital.

Table 4: Amount of summed ST segment elevations recorded at home and in hospital.

	Home ECG					
Hospital electrocardiogram	0 mm	0- 2 mm	2- 4 mm	4- 6 mm	> 6 mm	Total
0 mm	94	7	1	-	-	102
0- 2 mm	9	2	-	-	-	11
2- 4 mm	-	1	1	1	-	3
4- 6 mm	-	-	-	-	2	2
>6 mm	1	-	-	1	6	8
Total	104	10	2	2	8	126

Discussion

In this study, no major differences were found between home- and hospital derived ECG findings. In the early stages of acute cardiac pathology, ECG changes may fluctuate or subside permanently: ST depression or elevation may occur, or T waves invert. The ECG codes of 32 (25%) of 126 patients studied changed between recordings at home and hospital. However, the changes were restricted to the non-specific category and normal category. All patients with ST elevation or bundle branck block on their home recorded ECG had the same abnormalities on their hospital recorded ECG. This observation confirms that ST elevation occurs almost immediately after the onset of myocardial infarction and that such a diagnosis can be established electrocardiographically without delay. The rhythm abnormalities on the home ECG of 13 patients (10%) were not found on the recordings in the hospital; the supraventricular rhythm disturbances changed to normal sinus rhythms. The total amount of ST elevation decreased in 11 patients (9%) between the home and hospital recordings, but increased in 12 patients (9%). Only one patient with an initial normal ECG at home developed extensive ST segment elevations (> 6 mm) during transportation time to hospital. Therefore, this study demonstrates that an home recorded ECG can be used as a simple and reliable means of identifying patients with evolving cardiac pathology.

Few general practitioners use electrocardiography to diagnose myocardial infarction. A more widespread use of prehospital ECG recording will enable more general practitioners to treat patients with extensive myocardial infarction early with thrombolytic agents or select patients with a high probability of acute cardiac pathology for hospital admission. The electrocardiogram has a valuable role in the decision whether to give thrombolytic treatment. Recommendations as to which patients with chest pain should receive prehospital thrombolytic therapy have varied widely between the different reported studies, some reling on signs and symptoms

only,[8] while most require additional electrocardiographic criteria of infarction, such as ST segment elevation.[9-17]

The ability of general practitioners to accurately interpret electrocardiographic tracings may become increasingly important. However, most general practitioners do not regularly interpret electrocardiograms. McCrea assessed whether a representative sample of general practitioners could accurately identify electrocardiographic patterns which would help them to correctly use thrombolytic therapy.[18] In total, 82% of general practitioners correctly recognised a normal ECG. Recognition of acute abnormalities was less reliable. Acute ischemia was correctly identified between 33% and 61% of the general practitioners. Accurate localisation of the site of the infarct was achieved only in 8% to 30% of the participating general practitioners, while between 22% and 25% correctly interpreted non acute findings. The investigators concluded that the current level of proficiency of a sample of general practitioners in recognising acute myocardial infarction is insufficient and that refresher training is warranted. In the current study, computerized ECG recording was used by the ambulance nurses of the Municipal Health Service. This proved to be extremely valuable in these circumstances, where skilled readers were not immediately available. Such computerized interpretation of a prehospital electrocardiogram was safe and useful in the diagnostic classification of patients with chest discomfort.

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APPENDIX: PEP - FORMS

BEGELEIDINGSBRIEF CARDIALE PATIENTEN

INDICATIESTELLING PREHOSPITALE TROMBOLYSE

FORMULIER PREHOSPITAAL ECG PROJECT

Geachte huisarts,

Deze formulierset bestaat uit drie afzonderlijke gedeelten. Het eerste deel is de bekende begeleidingsbrief voor cardiale patiënten. In dit deel kunt U de gegevens nodig voor een optimale overdracht van Uw patiënt aan zowel de ambulancedienst als het ziekenhuis vermelden.

Het tweede deel bevat de indicatiestelling voor prehospitale trombolyse, inclusief ruimte voor het resultaat van de op alle ambulances van de GGD Rotterdam beschikbare computeranalyse van het ECG. De criteria zijn uitgebreid ten opzichte van het verleden om meer infarctpatiënten voor trombolytische behandeling vóór ziekenhuisopname in aanmerking te laten komen.

Het derde deel is het vragenformulier behorende bij het Prehospitale ECG project (PEP-project). Het doel van dit project is vast te stellen of de huisarts patiënten met aspecifieke thoracale klachten kan identificeren met behulp van een systematische anamnese, een lichamelijk onderzoek en een door een computerprogramma beoordeeld ECG. De achtergrond van dit project is te komen tot een meer efficiënte bezetting van de hartbewakingsbedden in Rotterdam en omstreken.

Wij verzoeken U deze formulierset zo volledig mogelijk in te vullen (met uitzondering van het gedeelte bestemd voor het resultaat van de computeranalyse) bij iedere patiënt die u voor cardiologische beoordeling c.q. opname naar het ziekenhuis doorverwijst, in afwachting van de aankomst van de ambulance. De gegevens worden uiteraard als medisch geheim beschouwd.

Bij voorbaat dankend voor Uw medewerking,

Ambulancedienst GGD Rotterdam.

I. **BEGELEIDINGSBRIEF CARDIALE PATIENTEN** Datum: |__|__|-|__|__|-|__|__|

Naam: Voorl: Geslacht: M/V Geboortedatum: Leeftijd: jr

Adres: Aanvragend arts:

SZR-verz./Part.-verz./Overig Verzekeringsnummer: Huisarts:

Voorgeschiedenis:

Andere klachten en aandoeningen:

Hoofdklacht:

Bestaande medicatie:

Begin klachten:	|__|__|:|__|__| u	Bloeddruk:	|__|__|/|__|__|__| mm	Medicatie	dosis	i.v./i.m.
Boodschap gestuurd:	|__|__|:|__|__| u	Polsfrequentie:	|__|__|__|/min	Thalamonal		
H.a. bij patiënt:	|__|__|:|__|__| u	Ritme:	Regulair/Irregulair	Lidocaïne		
GGD gewaarschuwd:	|__|__|:|__|__| u	Longoedeem:	Ja/Nee/Onbekend	Lasix		
Overleden om:	|__|__|:|__|__| u	Klamme huid:	Ja/Nee/Onbekend	Atropine sulf.		
Lichamelijk onderzoek:				Nitroglycerine		
				Adrenaline		

II. INDICATIESTELLING PREHOSPITALE TROMBOLYSE

1 MAAK ECG, UITSPRAAK APPARAAT NO. |__|__|:

Geen resultaat verkregen (ga naar 4)
Waarschijnlijk geen acuut groot hartinfarct* (ga naar 4)
Fors hartinfarct, start trombolytische behandeling* O

Overtuig U ervan dat de volledige 10 seconden ECG-signaal van alle 12 afleidingen van VOLDOENDE KWALITEIT is en dat DUIDELIJKE ST-ELEVATIES aanwezig zijn voordat U tot behandeling overgaat!

2 CONTROLEER INSLUITINGSCRITERIA:

	ja	nee
Pijn op de borst, typisch voor infarct, ≥ 30 min	O	(ga naar 4)
Pijn houdt aan na nitroglycerine sublinguaal	O	(ga naar 4)
Pijn minder dan 6 uur geleden begonnen.	O	(ga naar 4)

AANVANG KLACHTEN: |__|__|:|__|__| u

3 CONTROLEER CONTRA-INDICATIES:

	ja	nee
Leeftijd meer dan 75 jaar?	(ga naar 4)	O
Is er hartmassage toegepast?	(ga naar 4)	O
Is het bewustzijn van de patiënt verlaagd?	(ga naar 4)	O
Is er momenteel een verlamming aanwezig?	(ga naar 4)	O
Is de systolische bloeddruk ≥ 200 mm Hg?	(ga naar 4)	O

Vragen te stellen aan de patiënt	**ja**	**nee**
Bent U (mogelijk) zwanger?	(ga naar 4)	O
Lijdt u aan bloederziekte/stollingsziekte?	(ga naar 4)	O
Heeft U **OOIT** een beroerte gehad?	(ga naar 4)	O
Heeft U in **DE AFGELOPEN 3 MAANDEN**:		
a. een ernstig ongeluk gehad?	(ga naar 4)	O
b. een grote operatie ondergaan?	(ga naar 4)	O
c. bloed opgehoest?	(ga naar 4)	O
d. een maagbloeding of maagzweer gehad?	(ga naar 4)	O
e. bloed verloren bij ontlasting en/of urine?	(ga naar 4)	O
f. abnormaal vaginaal bloedverlies gehad?	(ga naar 4)	O
VANDAAG gevallen of het hoofd gestoten?	(ga naar 4)	O
Menstrueert U **OP DIT MOMENT**?	(ga naar 4)	O

Bij behandeling minder dan 1 jaar tevoren met streptokinase of Eminase mogen patiënten niet opnieuw met een van deze twee trombolytica worden behandeld. Stel daarom de volgende vragen aan de patiënt, alvorens tot behandeling met streptokinase of Eminase over te gaan:

	ja	nee
Heeft U **AFGELOPEN JAAR** voor een hartinfarct in het ziekenhuis gelegen?	(ga naar 4)	O
Bent U overgevoelig voor streptokinase of Eminase?	(ga naar 4)	O

Ingevuld door: huisarts/ambulancevplk

4 BESLUITVORMING:

Alleen indien aan **alle** voorwaarden voldaan is mag met trombolytische behandeling vóór ziekenhuisopname worden begonnen. Indien het resultaat van de ECG-analyse een indicatie voor trombolyse aangeeft maar behandeling vóór opname niet mogelijk of wenselijk is, geef dit dan via de CPA door aan het ziekenhuis onder vermelding van de redenen.

		ja	nee
• Past het ECG bij een groot infarct?	(vraag 1)	O	(ga naar 6)
• Alle insluitingscriteria aanwezig?	(vraag 2)	O	(ga naar 6)
• Geen contra-indicaties?	(vraag 3)	O	(ga naar 6)

5 START TROMBOLYSE VOLGENS PROTOCOL

Indien het infuus niet is gestart, wat was hiervoor de reden?

STAAK TROMBOLYSE BIJ HARTMASSAGE!

HOEVEELHEID TOEGEDIEND: |__|__|ml

6 VUL Prehospitaal ECG Project (PEP) FORMULIER IN

III. **PREHOSPITAAL ECG PROJECT**

Is er pijn of druk op de borst? ☐ Ja, hoofdklacht. ☐ Ja, nevenklacht. ☐ Nee Ga naar punt C)

Is de pijn of druk op dit moment nog steeds aanwezig? ☐ Ja Ga naar punt A) ☐ Nee Ga naar punt B)

A) Indien Ja: Hoe lang reeds aanwezig? ☐ 0-½ uur ☐ ½-3 uur ☐ 3-6 uur ☐ 6-48 uur ☐ > 48 uur

B) Indien Nee: Hoe lang is de patient klachtenvrij? ☐ 0-½ uur ☐ ½-3 uur ☐ 3-6 uur ☐ 6-48 uur ☐ > 48 uur

Hoe lang heeft de langste of ernstigste pijnaanval van de afgelopen 48 uur geduurd? ☐ 0-½ uur ☐ ½-1 uur ☐ 1-2 uur ☐ 2-4 uur ☐ > 4 uur

Indien er meerdere aanvallen zijn geweest, hebben de volgende vragen alleen betrekking op de langste of meest ernstige aanval.

	Ja	Nee	Onbekend
Is de pijn of druk midden en/of links op de borst gelokaliseerd?	☐	☐	☐
Is de pijn stekend van karakter?	☐	☐	☐
Is er uitstraling naar de hals, linker arm en/of linker schouder?	☐	☐	☐
Is er uitstraling naar de rug?	☐	☐	☐
Is er uitstraling naar de buik en/of (boven)benen?	☐	☐	☐
Is de pijn houdingsafhankelijk?	☐	☐	☐
Zit de pijn vast aan de ademhaling?	☐	☐	☐
Is er lokale drukpijn?	☐	☐	☐
Vermindert de pijn of druk op de borst binnen tien minuten na sublinguaal gebruik van (niet verouderde) nitroglycerine tabletten of nitroglycerine spray?	☐	☐	☐
Is de patient ooit eerder voor deze of soortgelijke klachten onder behandeling van een arts geweest?	☐	☐	☐
Berustten de klachten toen op angina pectoris of een hartinfarct?	☐	☐	☐

Hoe verhouden de klachten zich nu t.o.v. de vroegere angina pectoris? ☐ niet van toepassing ☐ minder ☐ ongeveer gelijk ☐ heviger ☐ onbekend

Hoe verhouden de klachten zich nu t.o.v. het vroegere hartinfarct? ☐ niet van toepassing ☐ minder ☐ ongeveer gelijk ☐ heviger ☐ onbekend

C)	Ja	Nee	Onbekend
Gaan de klachten gepaard met misselijkheid en/of braken?	☐	☐	☐
Gaan de klachten gepaard met dyspnoe?	☐	☐	☐
Gaan de klachten gepaard met transpireren?	☐	☐	☐
Is de patient in gezelschap van een persoon die alarm zou kunnen slaan in geval van nood, indien de patient de komende 12 uur thuis zou blijven?	☐	☐	☐

CONCLUSIE

Hoe schat u de kans in dat deze patient nu een hartinfarct heeft?

☐ zeer waarschijnlijk niet ☐ waarschijnlijk niet ☐ mogelijk ☐ waarschijnlijk wel ☐ zeer waarschijnlijk wel

Heeft deze patient op dit moment: ☐ geen angina pectoris ☐ stabiele a.p. ☐ onstabiele (de novo, toegenomen of in rust) a.p.?

Andere of bijkomende acute cardiale problemen (ritme stoornis, decompensatio cordis, enz):

_____

Voorlopige diagnose:

_____

Reden verwijzing ziekenhuis: ☐ sociaal ☐ beoordeling ☐ opname verpleegafdeling ☐ indicatie intensieve zorg

Als u op dit moment de beschikking had over een ECG met als uitslag: 'ECG zonder specifieke afwijkingen', zou u de patient verder thuis behandelen? ☐ Ja ☐ Nee ☐ Niet zeker

BEGELEIDINGSBRIEF CARDIALE PATIENTEN

INDICATIESTELLING PREHOSPITALE TROMBOLYSE

FORMULIER PREHOSPITAAL ECG PROJECT

Geachte collega,

Dit formulier bestaat uit drie afzonderlijke gedeelten. Het eerste deel is de bekende begeleidingsbrief voor cardiale patienten. In dit deel kunt U de gegevens nodig voor een optimale overdracht van uw patient aan zowel de ambulancedienst als het ziekenhuis vermelden.

Het tweede deel bevat de indicatiestelling voor prehospitale trombolyse, inclusief ruimte voor het resultaat van de op alle ambulances van de GGD Rotterdam beschikbare computeranalyse van het ECG.

Het derde deel is het vragenformulier behorende bij het Prehospitale ECG project (PEP-project). Het doel van dit project is vast te stellen of de huisarts patiënten met aspecifieke thoracale klachten kan identificeren met behulp van een systematische anamnese, een lichamelijk onderzoek en een door een computerprogramma beoordeeld ECG. De achtergrond van dit project is te komen tot een meer efficiënte bezetting van de hartbewakingsbedden in Rotterdam en omstreken.

Wij verzoeken U het formulier zo volledig mogelijk in te vullen (met uitzondering van het gedeelte bestemd voor het resultaat van de computeranalyse) bij iedere patiënt die u voor cardiologische beoordeling c.q. opname naar het ziekenhuis doorverwijst, in afwachting van de aankomst van de ambulance. De gegevens worden uiteraard als medisch geheim beschouwd.

Bij voorbaat dankend voor Uw medewerking,

E. van Loenen, arts, medisch leider,

Ambulancedienst GGD Rotterdam e.o.

BEGELEIDINGSBRIEF CARDIALE PATIENTEN Datum: |_|_|-|_|_|-|_|_|

Naam: Voorl: Geslacht: M/V

Adres: Geboortedatum: Leeftijd: jr

SZR-verz./Part.-verz./overig Verzekeringsnummer:

Aanvragend arts: Huisarts:

Voorgeschiedenis: Hoofdklacht:

Bestaande medicatie: Lichamelijk onderzoek:

	Uur: min		Medicatie	Dosis	i.v./i.m.
			Thalamonal	—	—
Begin klachten:	__ __ : __ __	Bloeddruk: ___ / ___	Lidocaine	—	—
Boodschap gestuurd:	__ __ : __ __	Polsfrequentie: ___	Lasix	—	—
H.a. bij patient:	__ __ : __ __	Ritme: regulair/irregulair	Atropine	—	—
GGD gewaarschuwd:	__ __ : __ __	Longoedeem: Ja/Nee/Onbekend	Adrenaline	—	—
Overleden om:	__ __ : __ __	Klamme huid: Ja/Nee/Onbekend	Overige	—	—
			Nitroglycerine s.l	—	

INDICATIESTELLING PREHOSPITALE TROMBOLYSE

1. MAAK ECG, APPARAAT No. |_|_|:

Geen resultaat verkregen	0 STOP
Geen bijzondere afwijkingen	0 Ga naar blz 2.
Mogelijk infarct of andere afwijking	0 Ga naar blz 2.
Groot hartinfarct, start trombolyse	0 Ga naar 2.

Overtuig U ervan dat de volledige 10-seconden ECG signaal van alle 12-afleidingen van VOLDOENDE KWALITEIT is en dat DUIDELIJKE ST-ELEVATIES aanwezig zijn voordat U tot behandeling overgaat!

2. CONTROLEER INSLUITINGSCRITERIA:	**Ja**	**Nee**
Pijn op borst, typisch voor infarct, ≥ 30 min	0	0 (STOP)
Pijn houdt aan na nitroglycerine sublinguaal	0	0 (STOP)
Pijn minder dan 6 uur geleden begonnen	0	0 (STOP)

3. CONTROLEER CONTRA-INDICATIES:	**Ja**	**Nee**
Leeftijd meer dan 75 jaar?	0 (STOP)	0
Is er hartmassage toegepast?	0 (STOP)	0
Is het bewustzijn van de patient verlaagd?	0 (STOP)	0
Is er momenteel een verlamming aanwezig?	0 (STOP)	0
Is de systolische bloeddruk ≥ 200 mm Hg?	0 (STOP)	0
Vragen te stellen aan de patient		
Bent U mogelijk zwanger?	0 (STOP)	0
Lijdt U aan een stollingsziekte?	0 (STOP)	0
Heeft U OOIT een beroerte gehad?	0 (STOP)	0
Heeft U in de AFGELOPEN 3 MAANDEN:	0 (STOP)	0
a. een ernstig ongeluk gehad?	0 (STOP)	0
b. een grote operatie ondergaan?	0 (STOP)	0
c. bloed opgehoest?	0 (STOP)	0
d. een maagbloeding of maagzweer gehad?	0 (STOP)	0
e. bloed verloren bij ontlasting en/of urine?	0 (STOP)	0
f. abnormaal vaginaal bloedverlies gehad?	0 (STOP)	0
VANDAAG gevallen of het hoofd gestoten?	0 (STOP)	0
Menstrueert U op DIT MOMENT?	0 (STOP)	0

Bij behandeling minder dan 1 jaar tevoren met streptokinase of Eminase mogen patienten niet opnieuw worden behandeld met een van deze twee trombolytica. Stel daarom de volgende vragen aan de patient, alvorens tot behandeling met streptokinase of Eminase over te gaan:

	Ja	Nee
Heeft U AFGELOPEN JAAR voor een hartinfarct in het ziekenhuis gelegen?	0 (STOP)	0
Bent U overgevoelig voor streptokinase of Eminase?	0 (STOP)	0

Indien een van deze vragen met "JA" wordt beantwoord, mag de patient niet behandeld worden met streptokinase.

Ingevuld door: huisarts/ ambulance-vpk

4. BESLUITVORMING:

Alleen indien aan ALLE voorwaarden is voldaan mag met trombolytische behandeling voor ziekenhuisopname worden begonnen. Indien het resultaat van de ECG analyse een indicatie voor trombolyse aangeeft maar behandeling voor opname niet mogelijk of wenselijk is, geef dit dan via de CPA door aan het ziekenhuis onder vermelding van de redenen.

Past het ECG bij een groot infarct? 0 ja 0 nee, STOP.
Alle insluitingscriteria aanwezig? 0 ja 0 nee, STOP.
Geen contra-indicaties? 0 ja 0 nee, STOP.

START TROMBOLYSE VOLGENS PROTOCOL

TIJDSTIP STARTEN INFUUS: |_|_| : |_|_|

STAAK TROMBOLYSE BIJ HARTMASSAGE!
HOEVEELHEID TOEGEDIEND: |_|_| ml.

PREHOSPITAAL ECG PROJECT

Verdenkt U de patient van een (mogelijk) infarct of instabiele angina pectoris? 0 Ja. Vul dit formulier in. 0 Nee, STOP.

Is er op dit moment sprake van pijn of druk op de borst? 0 Ja. 0 Nee, STOP.

Hoelang is de pijn of druk op de borst reeds aanwezig?
0 < 30 min
0 30 min- 3 uur
0 3-6 uur
0 > 6 uur

Vermindert de pijn of druk op de borst na nitroglycerine? 0 Ja 0 Nee 0 Onbekend

---

Geef in onderstaande tabel de antwoorden van de hieronder vermelde vragen en tel het aantal met "JA" beantwoorde vragen.

	Ja	Nee
1. Is er uitstraling naar de hals, linker arm en/of linker schouder?	0	0
2. Gaan de klachten gepaard met misselijkheid en/of transpireren?	0	0
3. Is er sprake van een cardiale voorgeschiedenis? (infarct, angina pectoris,PTCA, bypass-operatie)	0	0
4. Is de patient een man?	0	0

Aantal vragen met "JA" beantwoord is: | _ |

Hoe luidt de uitslag van het door de ambulance-verpleegkundige van de GGD vervaardigde ECG: | _ |

1. Geen bijzondere afwijkingen.
2. Mogelijk infarct of andere afwijking.
3. Groot hartinfarct, start trombolyse.

Is er een telefoon aanwezig? 0 Ja 0 Nee, opname geindiceerd.

Is de patient de komende uren in gezelschap van iemand die alarm kan slaan in geval van nood indien de patient thuis zou blijven? 0 Ja. Overweeg wel/ geen opname volgens tabel.
0 Nee. Opname altijd geindiceerd.

	ECG diagnose GGD		
Aantal met "JA" beantwoorde vragen uit de anamnese	Geen bijzondere afwijkingen	Mogelijk hartinfarct of andere afwijking	Groot hartinfarct, start trombolyse
0 x ja	Geen opname	Overweeg opname	Opname, overweeg trombolyse, volgens criteria blz.1.
1 x ja	Geen opname	Opname	
2 x ja	Overweeg opname	Opname	
3 x ja	Opname	Opname	
4 x ja	Opname	Opname	

"Geen opname" en "Overweeg opname" betekent dat: op grond van ervaringen in de regio Rotterdam deze patient waarschijnlijk geen acute cardiale problematiek heeft. Opname is dus wellicht niet nodig. Indien U de patient wel wilt laten opnemen, zal dit natuurlijk geschieden. **Het is uw beslissing!** Als U toch besluit tot opname van deze patient, wilt U dan hieronder uw belangrijkste reden opgeven:

_____

_____

SUMMARY

In the early 1960's Coronary Care Units were introduced to ensure prompt response to life-threatening arrhythmias in patients with evolving myocardial infarction. After introduction of thrombolytic therapy in the 1980's, treatment of patients with evolving myocardial infarction has improved significantly. The earlier treatment is initiated the better, which underlines the importance of early diagnosis. On the other hand, referral of patients without acute cardiac pathology should be avoided. Therefore, a rapid and reliable evaluation of patients with chest pain and other related symptoms is of paramount importance. This is the subject of this thesis.

In the Netherlands most patients are seen primarily by their general practitioner. Immediate recognition of evolving myocardial infarction in patients with chest pain is often difficult, in particular in general practice. The clinical information available for the general practitioner is often insensitive or nonspecific. If the diagnosis is uncertain, the general practitioners tend to refer patients to hospitals to "rule out myocardial infarction" rather than risk missing the diagnosis. This strategy ensures a high admission rate for patients with chest pain, but also leads to admission of many patients without acute cardiac pathology (myocardial infarction, unstable angina). Consequently, in 30-70% of the patients admitted to Coronary Care Units with symptoms suggestive of myocardial infarction, this diagnosis is not confirmed. If the differentiation of myocardial infarction and unstable angina pectoris from other causes of chest pain could be improved, the Coronary Care Units might be more effectively utilized. In Part I of this thesis, the selection of patients for hospital admission is described.

In chapter 1, various strategies for increasing the efficiency of managing patients with acute chest pain are reviewed. Some investigators, by use of predictive models, have tried to identify patients at low risk in the emergency department to minimize unnecessary admissions, whereas others have sought to identify patients with favourable prognoses for early transfer from the CCU to lower levels of care. A third strategy included the creation of a simple observation unit. Finally, it has been attempted to improve the diagnostic accuracy of the general practitioner; the main subject of this thesis.

In chapter 2, previously developed algorhythms to improve prehospital triage of patients with suspected acute cardiac disease were evaluated in a prospective study. All patients with symptoms of possible cardiac origin who were seen by a general practitioner and subsequently referred to hospital in the municipality of Rotterdam were included. Prior to hospital admission, symptoms of patients with suspected acute coronary disease were recorded by standardized questionnaire and a computerized ECG was made. In this first phase of the Prehospital ECG Project, all patients were hospitalized and a final diagnosis was established. A total of 1005 patients were studied, of whom 42% had myocardial infarction or unstable angina pectoris. Evaluation of previously developed algorhythms in this prehospital study

population resulted in an unsatisfactory diagnostic accuracy of these strategies. In a separate multivariable analysis, 6 characteristics from the history and an electrocardiogram appeared independently and significantly associated with acute cardiac pathology. The presence of an abnormal ECG proved to be the most important predictor. It is concluded that the hospital based algorhythms were not suitable for prehospital prediction of acute cardiac pathology. A new practical hospital admission model was developed, based on the 6 clinical predictors, including analysis of an electrocardiogram. Following appropriate validation, this out-of-hospital protocol may lead to better triage decisions by the general practitioner.

The results of the validation phase of the Prehospital ECG Project are presented in chapter 3. In the first phase, an algorhythm was developed based on the results from history and electrocardiogram analysis. By use of this algorhythm the general practitioner was able to determine the probability of acute cardiac pathology and could consequently decide if hospital admission was necessary. As from april 1993, this algorhytm was implemented in the Rotterdam Ambulance Service. Symptoms of patients with suspected myocardial infarction were recorded by a standardized questionnaire by the general practitioner and a computerized ECG was made. A total of 1020 patients were eligible. We obtained a final diagnosis on 977 patients and these patients were included in the analysis. In 750 (77%) patients, the decision rule adviced hospital admission. In total, 731 (98%) of these patients were referred to hospital. The diagnosis of acute cardiac pathology was confirmed in 57% of the patients. 19 patients (2%) were not hospitalized, mainly for social reasons, and 3 of these patients developed acute cardiac pathology, although no life-threatening complications (death, ventricular fibrillation, reinfarction) occurred. In 227 (23%) patients, the decision rule suggested "no or possible hospital admission". 99 (44%) of these patients were not hospitalized. No early complications occurred in these patients. In 7 patients (7%) a non-Q wave myocardial infarction was detected at the follow-up visit the next working day. These patients were then hospitalized but no in-hospital complications occurred. The results from this study indicated that prehospital triage by the general practitioner safely reduced the number of hospital admissions of patients without acute cardiac pathology without increased risk for the patients.

In chapter 4, an assessment was made of the economic consequences of the prehospital triage model as used by the general practitioner. We compared the costs for each of two management strategies. The first strategy comprised the admission of all patients to the CCU's with the exception of patients who were discharged from the emergency room directly (Phase I- Prehospital ECG Project). The second strategy included initial triage by the general practitioner, followed by assessment in the emergency room of the hospital (Phase II- Prehospital ECG Project). In the first phase, 100 patients (9%) were discharged home directly from the emergency room. The mean length of stay of the hospitalized patients was 7.0 days. In the second phase 166 patients (17%) were not hospitalized. 121 Patients (17%) were not hospitalized by the general practitioner and another 45 patients (5%) were

discharged home from the emergency room of the hospital. The mean length of stay of the hospitalized patients was also 7 days. A cost reduction of Dfl 39,632 per 100 patients was achieved by the additional triage decision of the general practitioner. Thus, a significant amount of money was economized by increasing the selection criteria for hospitalization by the general practitioner.

The application of prehospital thrombolytic therapy is described in Part II of this thesis. Early treatment with thrombolytic agents preserves left ventricular function and reduces mortality in patients with evolving myocardial infarction. Frequently however, in most patients there is an important delay before thrombolytic treatment can be initiated. Substantial time gain can be achieved by starting treatment before hospital admission. In chapter 5, an overview is presented of the 4 most important trials in which prehospital thrombolysis was initiated before hospital admission. The efficacy of prehospital treatment with thrombolytic agents was examined in the European Myocardial Infarction Project (EMIP). In this study, 5,469 patients were randomized to either prehospital or hospital initiated treatment with anistreplase and aspirin. Prehospital administration of thrombolytic agents resulted in a median time saving of 55 minutes, a 12% reduction in total mortality ($p=0.08$) and a 17% lower cardiac mortality at 30 days ($p=0.05$) compared to hospital treatment. The number of adverse reactions did not differ between the two groups. In the Myocardial Infarction Triage and Intervention Trial (MITI), hospital versus prehospital initiated thrombolytic therapy was conducted to determine whether prehospital intervention was feasible and safe. Significant benefit was associated with early thrombolytic treatment. Prehospital thrombolytic therapy was not associated with a higher frequency of complications. In de Grampion Region Early Anistreplase Trial (GREAT-study) in Scotland, the feasibility, safety and efficacy of domiciliary thrombolysis by the general practitioner was studied. Entry to the study was by strong clinical suspicion of acute myocardial infarction by the general practitioner. The patient was treated with thrombolytics (anistreplase) or placebo and transferred to hospital. The time gained by domiciliary administration of thrombolytic agents was considerable in this Scottish rural area and amounted to 2 hours. The time saving by domiciliary thrombolysis resulted in a 49% reduction of the 3 month mortality, with fewer Q-wave infarcts and better left ventricular function in the survivors. From the results it is concluded that prehospital treatment is feasible and safe, and life saving.

The fourth most important prehospital study is described in chapter 6, where the results of the REPAIR-study (REPerfusion in Acute Infarction Rotterdam) are presented. The purpose of this study was to assess the practical application and safety of prehospital thrombolytic intervention with either alteplase or streptokinase in patients with extensive myocardial infarction. In addition, the long term outcome has been determined. Included were all patients with chest pain of more than 30 minutes duration, presenting within 6 hours after symptom onset and with electrocardiographic evidence of extensive evolving myocardial infarction. Eligibility of patients was established by the general practitioner or the ambulance nurse using

a standardized questionnaire with (contra-) indications for thrombolytic therapy. Computerized ECG was recorded by ambulance nurses. In the presence of ST-segment elevation (sum ST elevation $\geq$ 1.0 mV in all leads), eligible patients received 100 mg alteplase (N= 246) or 50 mg alteplase in the ambulance followed by 750,000 IE streptokinase in hospital (N= 90), or 1,5000,000 IE streptokinase intravenously (N= 193).
From 1988-1993, 533 patients were eligible for prehospital thrombolytic treatment. 4 patients died before receiving thrombolysis. A total of 529 patients received prehospital initiated thrombolytic treatment. Mean time gained by prehospital administration of thrombolysis was 47 minutes. Overall, the rate of complications during transportation and during the first 24 hours after hospitalization was low. The cumulative survival rate at five years follow up was 92% and was similar among the different thrombolytic treatment regimens. It was concluded that prehospital administration of either alteplase or streptokinase is feasible and safe and results in significant time gain. The long term prognosis is excellent in spite of extensive evolving myocardial infarction upon admission.

In Part III, chapter 7, the results are presented of a comparison between prehospital ECG's recorded with the modified lead placement versus standard recordings of the entry ECG's in hospital. The purpose of this analysis was to verify the reliability of the prehospital recording system. The study population included all patients consecutively admitted to the University Hospital of Rotterdam, in whom a prehospital ECG was recorded. A total of 126 patients were entered in this sub-analysis for whom paired ECG's were available. The mean time interval between the electrocardiograms recorded prehospital and in hospital was 43 $\pm$ 38 minutes. The diagnosis of myocardial infarction was confirmed in 34 (27%) of the patients. Unstable angina pectoris was present in 30 (24%) patients. The most frequent ECG abnormality was ST depression in the prehospital recorded group and in the hospital recorded group. The ECG interpretation of 32 (25%) patients changed between recordings at home and hospital. The rhythm abnormalities on the home ECG in 13 patients (10%) were not found on the recordings in the hospital. The total amount of ST elevation decreased in 11 other patients (9%) between the home and hospital recordings, and increased in 12 patients (9%). No major differences were found between home- and hospital derived electrocardiographic findings in spite of the modified system for ECG lead placement. This study demonstrated that such computerized interpretation of a prehospital electrocardiogram was safe and useful in the diagnostic classification of patients with chest discomfort. Therefore, establishment of computerized ECG devices in the ambulances should be encouraged.

SAMENVATTING

In het begin van de jaren zestig werden de Hartbewakingseenheden opgericht teneinde adequate en spoedige hulp te kunnen bieden bij het behandelen en voorkomen van levensbedreigende ritmestoornissen bij patiënten met een ontwikkelend hartinfarct. Na de introductie van de trombolytica in de jaren tachtig zijn de mogelijkheden tot behandeling van patiënten met een hartinfarct aanzienlijk verbeterd. Hoe kleiner het tijdsverschil, dat verloopt tussen het begin van de klachten en het starten van trombolytische therapie, des te beter zijn de resultaten en de uiteindelijke prognose van deze behandeling. Daarom is vroege onderkenning van de diagnose hartinfarct van cruciaal belang. Dit vormt het onderwerp van dit proefschrift.

In de Nederlandse gezondheidszorgstructuur consulteren de meeste patënten met acute klachten eerst hun huisarts. Directe herkenning van de diagnose hartinfarct bij patiënten met pijn op de borst is soms niet eenvoudig, met name in de huisartsenpraktijk. De beschikbare klinische informatie is vaak ontoereikend om de diagnose met zekerheid te kunnen stellen. Als de diagnose niet zeker is neigen veel huisartsen in het algemeen tot opname van de patiënt in het ziekenhuis teneinde de diagnose hartinfarct uit te sluiten, dan het risico te lopen deze diagnose te missen. Dit leidt tot een toename van patiënten met pijn op de borst, en als gevolg daarvan ook tot een toename van opname van patiënten zonder acute cardiale pathologie. Bij 30-70% van de patiënten met pijn op de borst die opgenomen worden op de Hartbewakingseenheden kan de diagnose acute cardiale pathologie (hartinfarct of instabiele angina pectoris) niet bevestigd worden. Echter, indien de diagnoses hartinfarct en instabiele angina pectoris nauwkeuriger onderscheiden kunnen worden van andere oorzaken van pijn op de borst, kunnen de Hartbewakingseenheden efficiënter worden gebruikt.

In het eerste deel van dit proefschrift zal de identificatie van patiënten met acute cardiale pathologie worden beschreven.

In Hoofdstuk 1 worden verschillende methoden besproken die tot doel hebben de diagnostische nauwkeurigheid van acute cardiale pathologie en zijn complicaties te vergroten. Enkele onderzoeken hebben zich gericht op het bestuderen van de identificatie van patiënten met een grote of een kleine kans op acute cardiale pathologie op de Eerste Hulp afdeling van het ziekenhuis met gebruikmaking van verschillende beslismodellen. Andere studies hebben weer gezocht naar methoden om patiënten met een gunstige prognose binnen een bepaalde tijd (12- 24 uur) op de Hartbewakingseenheden te identificeren, hetgeen eerdere overplaatsing naar een cardiologische afdeling mogelijk maakt. Een derde strategie omvatte de oprichting van een eenvoudige observatie afdeling, alvorens patiënten op te nemen op de

Hartbewakingseenheden. Tenslotte is geprobeerd de diagnostische nauwkeurigheid van de huisarts te verbeteren; het voornaamste onderwerp van dit proefschrift.

In Hoofdstuk 2 worden de reeds eerder ontwikkelde beslisregels geëvalueerd teneinde de opname triage te verbeteren van patiënten met een mogelijk hartinfarct in een prospectieve studie. Alle patiënten in de regio Rijnmond met klachten van mogelijk cardiale origine, die hun huisarts consulteerden en vervolgens naar het ziekenhuis werden ingestuurd, kwamen in aanmerking. Voorafgaande aan de ziekenhuisopname werd door de huisarts bij iedere patiënt met klachten met verdenking op een hartinfarct een gestructureerde anamnese afgenomen met gebruikmaking van een vragenlijst, die onderdeel vormde van de cardiale begeleidingsbrief, die de huisarts toch al zou invullen indien een patiënt verwezen moest worden in verband met een cardiologische beoordeling. Door de ambulance dienst van de GGD werd met behulp van een draagbaar computer apparaat een ECG gemaakt. Vervolgens werden alle patiënten naar het ziekenhuis vervoerd. Van alle patiënten werd de uiteindelijke ontslagdiagnose verzameld. In totaal werden 1.005 patiënten bestudeerd in de eerste fase van het Prehospitaal ECG Project, waarvan 42% een hartinfarct of instabiele angina pectoris had. Toepassing van reeds bestaande in het ziekenhuis ontwikkelde beslisregels op deze prehospitale populatie resulteerde echter in een onvoldoende diagnostische nauwkeurigheid van deze beslismodellen. In een afzonderlijke multi-variate analyse bleken 6 variabelen afkomstig van de anamnese en het ECG onafhankelijk en significant geassocieerd te zijn met het voorspellen van de diagnose acute cardiale pathologie. De aanwezigheid van een abnormaal ECG bleek de meest voorspellende variabele. Hieruit kan men concluderen dat de op het ziekenhuis gerichte beslisregels niet geschikt zijn voor het voorspellen van acute cardiale pathologie in een prehospitale populatie. Een nieuw praktisch ziekenhuisopname model werd ontwikkeld, gebaseerd op de 6 klinische voorspellers, hetgeen ook de analyse van het ECG omvatte.

De resultaten van de validatie fase van het Prehospitaal ECG Project worden gepresenteerd in Hoofdstuk 3. In de eerste fase van het project werd een beslisregel ontwikkeld gebaseerd op gegevens afkomstig van de anamnese en het ECG. Door gebruikmaking van dit beslismodel werd de huisarts in staat gesteld de kans op acute cardiale pathologie te bepalen en aldus te besluiten of ziekenhuis opname inderdaad noodzakelijk was. Vanaf April 1993 werd dit beslismodel geïmplementeerd in de Rotterdamse Ambulance dienst. De anamnese van patiënten met een mogelijk hartinfarct werd afgenomen door de huisarts met behulp van een sterk vereenvoudigde vragenlijst, die de beslisregel omvatte. Vervolgens maakte de ambulance dienst van de GGD een ECG bij de patiënten thuis. In totaal kwamen 1.020 patiënten in aanmerking voor de studie. We verkregen een ontslagdiagnose van 977 patiënten en deze patiënten werden betrokken bij de uiteindelijke validatie van de beslisregel. Bij 750 patiënten (77%) voorspelde de beslisregel dat opname noodzakelijk zou zijn. 731 patiënten (98%) werden verwezen naar het ziekenhuis door de huisarts. De diagnose acute cardiale pathologie werd in 57% van de

patiënten bevestigd. 19 patiënten (2%) werden niet opgenomen op besluit van de huisarts, hoofdzakelijk vanwege sociale omstandigheden, waarvan slechts bij 3 patiënten sprake was van acute cardiale pathologie. Er hebben zich bij deze patiënten echter geen levensbedreigende complicaties (overlijden, ventrikelfibrilleren, recidief hartinfarct) voorgedaan. Bij 227 patiënten (23%) voorspelde de beslisregel dat opname niet nodig zou zijn. 99 patiënten (44%) werden alsnog niet opgenomen na besluit van de huisarts. Bij 7 patiënten (7%) werd de eerstvolgende werkdag na een follow-up bezoek van medewerkers van de STAR (Stichting Artsenlaboratorium Rotterdam) een non-Q infarct gedetecteerd. Deze patiënten werden alsnog in het ziekenhuis opgenomen, waarbij zich tijdens de opname geen complicaties hebben voorgedaan. De resultaten van deze studie indiceren dat prehospitale triage door de huisarts goed haalbaar en veilig is, en leidt tot een reductie van het aantal onnodige ziekenhuisopnames zonder toenemend risico voor de patiënt.

In Hoofdstuk 4 werd een schatting gemaakt van de financiële gevolgen van het prehospitale beslismodel, zoals gebruikt door de huisarts. We vergeleken de kosten voor elk van de 2 opname strategieën. De eerste strategie omvatte opname van alle patiënten op de Hartbewaking, met uitzondering van die patiënten, die direct vanaf de Eerste Hulp van het ziekenhuis naar huis waren ontslagen (Fase 1, Prehospitaal ECG Project). De tweede strategie omvatte de initiële triage door de huisarts, gevolgd door evaluatie van de patiënt op de Eerste Hulp afdeling van het ziekenhuis (Fase 2- Prehospitaal ECG Project). In de eerste fase werden 100 patiënten (9%) direct vanaf de Eerste Hulp naar huis ontslagen. De gemiddelde opname duur van de gehospitaliseerde patiënten bedroeg 7 dagen. In de tweede fase van het onderzoek werden 166 patiënten (17%) niet opgenomen. 121 patiënten (12%) werden thuis gelaten door de huisarts en de andere 45 patiënten (5%) werden vanaf de Eerste Hulp van het ziekenhuis naar huis ontslagen. De gemiddelde opname duur van de gehospitaliseerde patiënten bedroeg eveneens 7 dagen. Een winst van F 39.632 per 100 patiënten werd bereikt door verbetering van de opname criteria door de huisarts en aldus kan een belangrijke hoeveelheid geld worden bespaard door toepassing van een dergelijke beslisregel.

Deel 2 van dit proefschrift beschrijft de toepassing van trombolytische behandeling voor opname in het ziekenhuis. Vroege behandeling met trombolytica leidt tot maximaal behoud van de linkerkamer functie en reduceert de sterfte bij patiënten met een ontwikkelend hartinfarct. Vaak gaat er echter veel tijd verloren eer men tot behandeling kan overgaan. Extra tijdwinst kan bereikt worden door de behandeling reeds voor ziekenhuis opname toe te dienen. In Hoofdstuk 5 wordt een overzicht gegeven van de 4 grootste en belangrijkste onderzoeken op het gebied van prehospitale trombolyse. De effectiviteit van prehospitale behandeling met trombolytica werd uitgebreid bestudeerd in de EMIP (European Myocardial Infarction Project) studie. In deze studie werden 5.469 patiënten gerandomiseerd tot behandeling met anistreplase en aspirine voor ziekenhuisopname of na ziekenhuisopname. Toediening van trombolytica voor ziekenhuisopname resulteerde in een mediane tijdwinst van 55 minuten, een 12% reductie in de sterfte (p= 0.08)

en een 17% lagere cardiale sterfte na 30 dagen (p= 0.05) in vergelijking met toediening na ziekenhuis opname. Het aantal bijwerkingen verschilde niet tussen beide groepen. In het MITI project (Myocardial Infarction Triage and Intervention Trial) werd eveneens bestudeerd of toediening van trombolytica voor ziekenhuisopname haalbaar en veilig is. Vroege toediening van trombolytica was geassocieerd met een significante winst in overleving. Prehospitale toediening van trombolytica ging niet gepaard met een toename van het aantal complicaties. In de Grampion Region Early Anistreplase Trial (GREAT-studie) in Schotland werd het effect van het toedienen van trombolytica door de huisarts bij de patiënt thuis bestudeerd. Patiënten bij wie de huisarts sterk het vermoeden had dat er sprake zou kunnen zijn van een hartinfarct kwamen in aanmerking. De huisarts vervaardigde zelf een ECG, alhoewel er geen strikte ECG criteria werden geëist om patiënten al dan niet in de studie op te nemen. Vervolgens werd de patiënt behandeld met een trombolyticum (anistreplase) of een placebo en naar het ziekenhuis vervoerd. Indien thuis placebo was toegediend ontving de patiënt alsnog het trombolyticum in het ziekenhuis en omgekeerd. In de thuis behandelde groep werd 61% van de patiënten binnen 2 uur behandeld versus slechts 0.6% in de ziekenhuis groep. De tijdwinst behaald met het geven van trombolyse thuis in deze Schotse plattelands-regio was groot en bedroeg 2 uur. Na 3 maanden waren 13 van de 163 patiënten in de prehospitale groep overleden (8%) versus 23 (16%) in de controle groep van 148 patiënten. Bovendien was er sprake van een significante vermindering van het aantal Q-golf infarcten en trad er minder beschadiging van de linkerkamer op bij de overlevenden in de prehospitale groep.

In Nederland werd het REPAIR-onderzoek (REPerfusie bij Acute Infarcten in Rotterdam) opgezet om de haalbaarheid van trombolyse voor ziekenhuisopname te bestuderen. De resultaten van deze studie worden gepresenteerd in Hoofdstuk 6. De indicatie voor trombolytica wordt gesteld door de huisarts dan wel door de ambulance-verpleegkundige van de GGD met behulp van een korte vragenlijst, waarop de indicaties en de contra-indicaties voor toediening van trombolytica zijn aangegeven. Een klein draagbaar ECG-apparaat wordt gebruikt om ter plaatse de aanwezigheid van een groot hartinfarct vast te stellen (som ST elevatie in alle afleidingen $\geq$ 1.0 mV). Vervolgens wordt de patiënt behandeld met alteplase of streptokinase en vervoerd naar het ziekenhuis. Sinds de aanvang van het onderzoek in 1988 zijn 246 patiënten volledig behandeld met alteplase, 90 patiënten gedeeltelijk behandeld met alteplase in de ambulance, gevolgd door streptokinase in het ziekenhuis en 193 patiënten behandeld met uitsluitend streptokinase. Om de tijdwinst te bepalen, die behaald werd door toedienen van trombolytica voor opname in vergelijking met toediening tijdens ziekenhuis opname, werd een vergelijking gemaakt met een groep die vervoerd was zonder dat er een indicatie was voor prehospitale behandeling, maar die op het moment van opname in het ziekenhuis wel voor trombolyse in aanmerking kwam. Deze controle groep bestond uit 220 patiënten, merendeels oudere patiënten of patiënten met een kleiner infarct. Bij de 529 patiënten die sinds 1988 behandeld werden met alteplase en/of streptokinase

bedroeg de mediane tijdwinst 47 minuten. Het aantal complicaties tijdens het transport naar het ziekenhuis was laag zowel in de met alteplase als in de met streptokinase behandelde groep. De prognose van de behandelde patiënten was goed. Totaal overleed in de eerste 24 uur slechts 2% van de patiënten in de thuis behandelde groep en 8% van de patiënten na 5 jaar.

In Deel III, hoofdstuk 7 van dit proefschrift, worden de resultaten gepresenteerd van de vergelijking tussen de prehospitale ECG's gemaakt met het computer ECG apparaat versus de standaard ECG opnames in het ziekenhuis. Het doel van deze analyse was het verifiëren van de betrouwbaarheid van de prehospitale ECG diagnostiek. De studie populatie omvatte alle patiënten die opgenomen werden in het Academisch ziekenhuis Dijkzigt en bij wie een prehospitaal ECG was gemaakt. In totaal waren 126 patiënten beschikbaar voor deze sub-analyse, waarbij zowel de prehospitale ECG's beschikbaar waren als de eerste opname ECG's gemaakt op de Eerste Hulp afdeling van het Academisch Ziekenhuis Dijkzigt. De gemiddelde tijd verstreken tussen beide ECG's bedroeg 43 ± 38 minuten. De meest frequente ECG bevinding was het voorkomen van ST segment depressie in zowel de prehospitale als de ziekenhuis groep. De ECG interpretatie van 32 patiënten (25%) verschilden tussen de opnames thuis en in het ziekenhuis. De ritme afwijkingen van 13 patiënten (10%) die werden gevonden op het prehospitale ECG, werden niet meer gezien op het ziekenhuis ECG. In vergelijking met de prehospitale ECG's en de ziekenhuis ECG's nam de totale som van de ST segment elevaties af bij 11 patiënten (9%) en nam toe bij 12 andere patiënten (9%). Er werden geen belangrijke verschillen gevonden tussen de thuis en in het ziekenhuis vervaardigde ECG's ondanks het afwijkende systeem zoals gebruikt in de thuis situatie. Deze studie toonde aan, dat een thuis vervaardigd ECG gebruikt kan worden als een simpele en bruikbare methode om patiënten te classificeren met klachten verdacht van een hartinfarct. Toepassing van prehospitale ECG diagnostiek in de ambulances buiten de regio Rotterdam kan dus worden aanbevolen!

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CURRICULUM VITAE

Els Grijseels is geboren op 15 december 1959 te Rotterdam. Na het behalen van het Atheneum-B diploma in 1978 volgde zij het Propedeuse jaar van de opleiding Diëtetiek te Den Haag. In 1979 begon zij aan de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam, alwaar zij in 1986 het artsexamen behaalde. Vanaf 1986 was zij werkzaam als Algemeen arts-assistent en Cardiologie assistent in het van Dam- Bethesda ziekenhuis. Vervolgens was zij werkzaam als arts-assistent Cardiologie in het Zuiderziekenhuis in Rotterdam (opleider: Dr. X.H. Krauss). Vanaf 1990 volgde zij de twee-jarige opleiding tot huisarts aan het Rotterdams Universitair Huisartsen Instituut. Tijdens deze opleiding werkte zij enige maanden op de afdeling Epidemiologie & Biostatistiek van de Erasmus Universiteit Rotterdam aan een onderzoek naar "Orthostatische hypotensie bij jongeren", onder begeleiding van Prof. Dr. D.E. Grobbee. Na de huisartsen-opleiding was zij werkzaam op de afdeling Klinische Epidemiologie van het Thoraxcentrum van het Dijkzigt ziekenhuis en op het Rotterdams Universitair Huisartsen Instituut, waar zij projectcoördinator was van het Prehospitaal ECG Project.

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