The HEART score for chest pain patients

De HEART score voor patiënten met pijn op de borst

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ISBN 978-90-8891-419-5

Printed & lay-out by: Proefschriftmaken.nl || Printyourthesis.com
Published by: Uitgeverij BOXPress, Oisterwijk

Sponsoren:

Gold
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The HEART score for chest pain patients

De HEART-score voor patiënten met pijn op de borst

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, volgens het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 20 juni 2012 om 2.30 uur

door

Barbra Backus

geboren op 14 december 1979 te Eindhoven

Promotor: Prof. dr. P.A.F.M. Doevendans

Co-promotor: Dr. A.J. Six

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Part Five
Summary and acknowledgements

General introduction

Cardiovascular diseases are the leading cause of death in the Netherlands. Each year around 50,000 patients with chest pain present in an emergency department (ED). An average hospital in the Netherlands treats 5-10 new cases per day. It is the role of the treating physician to distinguish an acute coronary syndrome (ACS) from a variety of other cardiac and non-cardiac diseases that may cause chest pain. In a number of cases, a diagnosis can be made quickly, in particular in case of ST-segment elevation acute myocardial infarction (STEMI). However, STEMI patients represent only a small percentage of all chest pain patients seen at the ED. A variety of other diseases may mimic ACS, such as pleural and pericardial irritations, gastro-intestinal reflux, pulmonary embolism, hyperventilation, musculoskeletal pain and cholecystitis[1,2,3].

Due to the high case fatality of acute myocardial infarction (AMI) and clear improvement in prognosis following timely interventions, early recognition of AMI and ACS remains essential. However, the challenge in the ED is not only to identify patients at the highest risk, but also to identify patients with non-urgent diseases or even the absence of disease. These patients may be discharged immediately with minimal testing or intervention. Clearly, when treated as an ACS, the latter will be prone to unnecessary risks of various treatments, such as the side effects of medication or radiation of a CT scan. In addition, redundant clinical observation periods cause the occupation of hospital beds and associated medical costs. With the increasing age of the population and advancing medical techniques, healthcare costs are a critical issue in many countries. Awareness of these costs as well as treatment risks is necessary before considering a certain strategy for the individual patient[1].

The diagnosis of ACS is confirmed in the vast majority of cases where significant ECG changes and/or increased levels of myocardial markers in plasma are present. However, absence of

such abnormalities doesn't exclude ACS. Therefore, for many physicians, the diagnosis of ACS is felt to be difficult to exclude in the early stage of the diagnostic process. It is important to make the diagnosis quickly, as patients benefit significantly from early treatment[3]. Recent guidelines suggest the use of well-developed and validated risk scores, to stratify patients at the ED and to make timely decisions in the emergency setting[1,4].

Risk scores

In literature several risk scores for patients with ACS have been published. In clinical practice, simple risk scores may be favourable, in particular when they can be calculated at the patient's bedside. The ideal risk score closely follows clinical thinking to facilitate applicability and interpretation. In this thesis the applicability of the PURSUIT score (2000)[5], the TIMI risk score (2000)[6], the GRACE score (2003)[7,8,9] and the FRISC score (2004)[10] are discussed in **chapter 2**. Notwithstanding the firm scientific basis of all four scoring systems, none is generally applied in all hospitals, despite the recommendations in the guidelines[11]. All four scoring systems were designed for identifying patients in the coronary care unit who were at the highest risk of an ACS or an adverse outcome. These scores were not designed for early differentiation within the vast majority of chest pain patients in the ED who are at low to moderate risk for an adverse outcome.

In 2007 the HEART score was developed, which was specifically designed for all chest pain patients at the ED[12,13]. The composition of the HEART score was not preceded by a multivariate regression analysis as modern scores often are, but was based on clinical experience and medical literature. The HEART score was designed to be as easy to use as the Apgar score for newborns[14]. The HEART score for chest pain patients in the ED incorporates all five elements of clinical judgment: History, ECG, Age, Risk factors and Troponin. By appreciating each of these five elements with 0, 1 or 2 points, each patient will receive

a score of 0-10. Validation studies of the HEART score are described in **chapter 3, 4 and 5**.

Worldwide differences

External validation studies of risk scores outside the original derivation and validation centers are uncommon. However, they are important in order to assess the applicability of the risk scores in other locations and populations. In **Chapter 6** is described how the HEART score was validated on a database of ten countries in the Asia-Pacific region. These data are remarkably consistent with the results of the Dutch validation studies.

Chapter 7 describes the combined results of the retrospective validation, the prospective validation and the Asia-Pacific validation studies.

Development of Risk scores

The most objective method for model derivation is through statistical analysis of a large cohort of patients, particularly to obtain estimates of strength of different predictive effects. Since the HEART score was designed in the absence of statistical analysis of empirical data, our aims were to assess the predictive effects of the five HEART components in patient data of our multicentre prospective study and to compare the performance of a model based on regression analysis with the performance of the original HEART score. The results of this study are given in **Chapter 8**.

Additional testing

In daily practice more than 80% of chest pain patients are admitted to the coronary care unit or chest pain unit for clinical observation, additional diagnostics or treatment. However, in only around 20% of these patients a major adverse cardiovascular event (MACE) occurs, consisting of AMI, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or death[12,13]. Early and adequate rule out of AMI and ACS is

important in view of the costs (e.g. ambulance, diagnostic procedures, hospital admissions), patient burden involved and adequate use of limited hospital beds. In very recent literature it was suggested by Mahler[15] and coworkers that a bicycle exercise test does not differentiate the risk of a non-STE-ACS in low-risk patients (that is, patients with negative initial biomarkers and normal or nondiagnostic ECGs). Khare[16] et al also discussed the diagnostic uncertainty of stress tests in low risk patients and reported additional costs of $5736 in those low risk patients with a positive or indeterminate stress test who underwent subsequent catheterization.

Furthermore, Mahler suggested that serial cardiac biomarkers increase the diagnostic performance of the HEART score. This idea was also addressed by Goodacre[17] et al, who investigated usefulness of additional tests in patients with chest pain. According to their results serial biomarker testing could increase the sensitivity for rule out of ACS. Four sub studies have been performed against this background.

Chapter 9 addresses the question whether a bicycle exercise test is a valuable and accurate diagnostic test in patients with suspected ACS, after they have been divided into low, intermediate and high-risk categories by performing the HEART score. Based on our validation studies, it may be concluded that the HEART score is a reliable predictor of cardiovascular events. The questions is whether additional exercise testing ads diagnostic value.

In **Chapter 10 and 11** the overall medical consumption after presentation in the ED is described. Health care costs in the Netherlands have risen dramatically in the last decade. Strategies are needed to reduce costs, for example by diagnosing and treating patients more accurately. In case of chest pain patients, clinicians tend to postpone the process of decision-making. They admit patients for clinical observation, meanwhile treating them for ACS awaiting final diagnosis. One hospital bed-day on a normal ward in a general hospital costs €435, and one day on the

intensive care unit costs €2183. Accurate identification of low risk patients, who do not need any further work-up, may save the use of resources, and consequently, money.
Chapter 12 concerns the value of a second, representative Troponin test in patients presenting to the ED. Very often if the episode of chest pain occurred within six hours before presentation patients are admitted to the coronary care unit to measure a second Troponin level. The three validation studies of the HEART score have been performed with the first Troponin sample only. The question is whether the diagnostic accuracy of the HEART score increases, when a Troponin level is used, taken six hours after complaints.

Conclusion

In summary, in today's practice, approximately 80% of chest pain patients in the ED have no clear ACS at presentation[13]. Clinicians tend to postpone the decision making process and to admit these patients for clinical observation, meanwhile treating them for an ACS. Consequently, over diagnosis and unnecessary treatment are common, resulting in redundant patient burden and high cost. In order to improve risk stratification of chest patients in the emergency department and to place relative arguments for ACS into perspective, we designed the HEART score.

The HEART score improves risk stratification in patients presenting with chest pain at the ED. In patients identified as low risk, additional test might be redundant. Diagnostic pathways may be improved and health care costs reduced when the HEART score is applied for chest pain patients in the ED.

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Chapter 2

Risk scores for patients with chest pain: evaluation in the emergency department

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***Current Cardiology Reviews,* 2011, *7,* 2-8**

ABSTRACT:

Chest pain is a common reason for presentation to the emergency department (ED). Absolute criteria for Acute Coronary Syndrome without ST elevation (NSTE-ACS) are lacking. An acute coronary syndrome (ACS) needs to be distinguished from a variety of other cardiac and non-cardiac diseases that may cause chest pain.
For patients with confirmed ACS, several scoring methods can be applied in order to distinguish patients in the coronary care unit who may benefit most from therapies. The PURSUIT, TIMI, GRACE and FRISC risk scores are well validated with this respect. However, none of these risk scores has been used in the identification of an ACS in the emergency setting. The vast majority of patients with chest pain due to causes other than ACS were not evaluated in these trials. An evidence-based systematic stratification and policy for these patients does not currently exist.

The more recently developed HEART score is specifically designed to stratify all chest pain patients in the ED. The HEART score was validated in a retrospective multicenter study and proved to be a strong predictor of event free survival on one hand and potentially life threatening cardiac events on the other hand. The HEART score facilitates risk stratification of chest pain patients in the ED.

INTRODUCTION

Chest pain is one of the most common reasons for patients to present to the emergency department (ED). An acute coronary syndrome (ACS) needs to be distinguished from a variety of other cardiac and non cardiac diseases that may cause chest pain. In a number of cases, a diagnosis can be made quickly, in particular in case of ST-segment elevation acute myocardial infarction (STEMI). However, STEMI patients represent only a small percentage of all chest pain patients in this setting. A variety of other diseases may mimic ACS, such as pleural and pericardial irritations, gastro-intestinal reflux, pulmonary embolism, hyperventilation, musculoskeletal pain and cholecystitis[1-3].

The challenge in the ED is not only to identify patients at the highest risk, but also to identify patients with non-urgent diseases or even the absence of disease. These patients may be discharged immediately with minimal testing or intervention. Clearly, when treated as ACS, the latter will be prone to unnecessary risks of various treatments, including the side effects of medication or radiation. In addition, this causes the occupation of hospital beds through admission of such patients and associated increase in medical costs. With the population's increasing age and advancing medical techniques, healthcare costs are a critical issue in many countries. Awareness of these costs as well as treatment risks is necessary before considering a certain strategy for the individual patient [2].

Regarding patients with ACS, the diagnosis is confirmed in the vast majority of cases where significant ECG changes such as STEMI and/or increased levels of myocardial markers in plasma are present. However, absence of such abnormalities doesn't exclude ACS. Therefore, the diagnosis of ACS is felt to be difficult to exclude in the early stage of the diagnostic process. It is important to make the diagnosis quickly, as patients benefit significantly from early treatment [3]. With this perspective in mind and the possible life threatening character of ACS, guidelines for chest pain patients are mainly focused on the identification of those patients at the highest risk of an ACS. High risk patients will benefit most from early aggressive therapies. With this approach, the current guidelines disregard

the many chest pain patients with a wide selection of non-urgent diagnoses in whom admission is not necessary.

Risk Scores

Several scoring methods are developed in order to distinguish patients in the ED or coronary care unit at the highest risk of an ACS or an adverse outcome, who may benefit most from aggressive therapies.

PURSUIT

The PURSUIT score (2000) was developed in a multinational randomized clinical trial (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy), with 9,461 patients, comparing eptifibatide (Integrilin) to placebo in the management of Unstable Angina (UA) or NonST-elevation Myocardial Infarction (NSTEMI) [4]. By use of multivariate regression analysis the investigators identified seven risk predictors for death and myocardial infarction (MI) in patients with acute coronary syndromes. Five of these risk factors were then combined into a scoring system: higher age, sex, worst Canadian Cardiovascular Society (CCS) class of angina, signs of heart failure and ST-segment depression on the index ECG. The investigators did not include tachycardia and low systolic blood pressure in the final risk score (Table 1). Scoring each of the five elements results in a possible score ranging from 1 to 18. The PURSUIT score predicts the risk of death or death/MI at 30 days after admission. According to the PURSUIT score ACS patients are divided into low, intermediate and high risk patients, with suggested therapies of early discharge, “watchful waiting” and aggressive antiplatelet / early invasive strategies respectively. The c-statistic of the original study for predicting the primary endpoint was 0.84 for death alone and 0.67 for the composite endpoint of death/MI.

Table 1. Composition of the PURSUIT Risk Score for UA

Age (decade)	50	8	
	60	9	
	70	11	
	80	12	
Sex	Male	1	
	Female	0	
Worst CCS class past 6 weeks	No angina/ CCS I/II	0	
	CCS III/IV	2	
Signs of heart failure		2	
ST depression on ECG		1	
		Total	

UA = Unstable Angina, CCS = Canadian Cardiovascular Society

TIMI

The TIMI risk score (2000) is derived from the Thrombolysis In Myocardial Infarction (TIMI)-11B trial, a multinational, randomized clinical trial, comparing unfractionated heparin to enoxaparin, which included all patients with confirmed ACS [5]. Data from 1,957 patients enrolled in the unfractionated heparin group were used to identify twelve elements of typical ACS findings by use of multivariate regression analysis. Seven of these elements remained statistically significant in a multivariate analysis. Together these seven elements compose the TIMI score for unstable angina/NSTEMI: age > 65 years, ≥ 3 classical risk factors for coronary artery disease (CAD), known CAD, use of Aspirin in the past 7 days, severe angina in the past 24 hours, elevated cardiac markers and ST-deviation 0.5 mm (Table 2). Each of these elements can be assigned with 0 or 1 points, resulting in a score of 0-7. The TIMI score predicts the risk of all cause mortality, MI and severe recurrent ischemia requiring urgent revascularization within 14 days after admission as well as benefit of enoxaparin.

Table 2. Composition of the TIMI Score for UA/NSTEMI

Historical		
Age > 65 years	0	
	1	
≥ 3 risk factors for CAD	0	
	1	
Known CAD (stenosis ≥ 50%)	0	
	1	
ASA use in past 7 days	0	
	1	
Presentation		
Recent (≤ 24H) severe angina	0	
	1	
↑ cardiac markers	0	
	1	
ST deviation ≥ 0.5 mm	0	
	1	
	Total	

NSTEMI = Non-ST-segment Elevation Myocardial Infarction, CAD = Coronary artery disease, ASA = Acetyl Salicylic Acid

Event rates increased significantly with increasing TIMI-scores. According to the TIMI score patients are divided into low (score 0-2), intermediate (score 3-4) and high (score 5-7) risk categories. The c-statistic of the TIMI score in the original trial was 0.65. The TIMI score was validated internally and externally in the enoxaparin group of the TIMI 11B trial and in both groups of the ESSENCE trial [5]. This validation showed comparable results with a mean c-statistic of 0.63. In addition the TIMI score is validated in several other databases and was compared with other scoring systems [6-8]. In various succeeding trials the TIMI risk score was applied in analyzing treatment efficacy in various ACS risk groups.

GRACE

The GRACE score (2003) was developed in a multinational registry of 11,389 ACS patients (Global Registry of Acute Coronary Events) [9-10]. Registration was performed prospectively and retrospectively. Patients who died within 24 hour after admission were excluded. After data collection, by use of multivariate logistic regression analysis, the investigators identified eight independent risk factors for inhospital death and post-discharge death at 6 months. These risk factors were then combined into a scoring system, consisting of hemodynamic, laboratory, ECG and patient specific findings: Killip class for congestive heart failure (CHF), systolic blood pressure at presentation (SBP), heart rate at presentation (HR), age, creatinine level, cardiac arrest at admission, ST-segment deviation on the index ECG and elevated cardiac enzyme levels. Each element has its own scoring, resulting in a possible score ranging from 1 to 372 (Table 3).

Table 3. Composition of the GRACE Score (2003)

1. Find Points for Each Predictive Factor:

Killip Class	Points	SBP, mm Hg	Points	Heart Rate, Beats/min	Points	Age, y	Points	Creatinine Level, mg/dL	Points
I	0	≤80	58	≤50	0	≤30	0	0-0.39	1
II	20	80-99	53	50-69	3	30-39	8	0.40-0.79	4
III	39	100-119	43	70-89	9	40-49	25	0.80-1.19	7
IV	59	120-139	34	90-109	15	50-59	41	1.20-1.59	10
		140-159	24	110-149	24	60-69	58	1.60-1.99	13
		160-199	10	150-199	38	70-79	75	2.00-3.99	21
		≥200	0	≥200	46	80-89	91	>4.0	28
						≥90	100		

Other Risk Factors	Points
Cardiac Arrest at Admission	39
ST-Segment Deviation	28
Elevated Cardiac Enzyme Levels	14

2. Sum Points for All Predictive Factors:

Killip Class	+	SBP	+	Heart Rate	+	Age	+	Creatinine Level	+	Cardiac Arrest at Admission	+	ST-Segment Deviation	+	Elevated Cardiac Enzyme Levels	=	Total Points

Event rates increased significantly with increasing GRACE-scores, ranging from 0.2% to 52% chance of inhospital death. The investigators did not divide patients into different risk categories. However, the individual risk of inhospital death may be used for optimal triage and management.

The c-statistic of the GRACE score in the original database was 0.83. The GRACE score was directly validated in a subsequent cohort of 3,972 patients and in 12,142 patients enrolled in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO)-IIb trial [11]. This validation showed comparable results with c-statistic results of 0.84 and 0.79 respectively. The c-statistics were similar for patients with (0.83) and without (0.82) ST segment deviation, with (0.81) and without (0.83) elevated cardiac markers and for patients younger than 65 years (0.78) or older than 65 years of age (0.82).

In addition, the GRACE score has been validated in several other databases [9] and was compared with other scoring systems in various succeeding trials [6-8].

FRISC

The FRISC score (2004) is based on the FRISC (Fast Revascularisation in Instability in Coronary disease) II trial [12]. A multicenter, randomized clinical trial, which included patients with unstable coronary artery disease. By use of multivariate regression analysis data from 1,235 patients enrolled in the non-invasive cohort were used to identify seven parameters as independent predictors of death/MI in patients with unstable angina. Together these seven parameters compose the FRISC score, consisting of age ≥ 70 years, male gender, diabetes, previous MI, ST-segment depression on admission, elevated levels of Troponin and elevated levels of Interleukin 6 or CRP (Table 4). Each of these elements can be appreciated with 0 or 1 points, resulting in a score of 0-7. The c-statistic of the FRISC score for the prediction of death was 0.77 and for death/MI 0.70. Using different age cut offs had only minimal effect on the accuracy. Use of CRP alone instead of CRP and Interleukin-6 decreased the c-statistics to 0.76 and 0.68 respectively.

Patients were categorized into low, intermediate and high risk, based on the FRISC scores of 0-2, 3-4 and 5-7. The FRISC score is the only risk score that focused on the treatment effect of early invasive strategies in ACS. To evaluate this effect the developed risk score was also per- formed on the invasive cohort with 1,222 patients. In the high risk group mortality reduced from 15.4 – 5.2%, while the composite endpoint of death and MI was reduced in both intermediate and high risk groups. Therefore, investigators recommended early invasive strategies for patients with a FRISC score ≥ 3.

Table 4. Composition of the FRISC Risk Score for UA

Age70 years	0
	1
Male sex	0
	1
Diabetes	0
	1
Previous MI	0
	1
ST depression on ECG	0
	1
Elevated Troponin levels	0
	1
Elevated Interleukin 6 or CRP	0
	1
Total	

HEART

Recently (2008), the HEART risk score was developed for chest pain patients presenting to the ED [13,14]. The composition of the HEART score was not based on multivariate regression analysis but on the decision making clinical factors according to expert opinion. The HEART score is composed of five

parameters of clinical judgement: History, ECG, Age, Risk factors and Troponin. By appreciating each of these five elements with 0, 1 or 2 each patient patients will receive a score of 0-10 (Table 5).

The HEART score was consecutively validated in a single center retrospective study in 122 patients [13] and a multicenter retrospective investigation in 880 patients [14]. These studies were conducted in all patients presenting to the ED for chest pain within the first quarter of 2006. No other inclusion or exclusion criteria were used. The investigators calculated the predictive value of the HEART score for the combined endpoint of MI, Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG) or death within 6 weeks after presentation.

Table 5. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Event rates increased significantly with increasing HEART scores. The c-statistic was 0.90, indicating good to excellent discriminative power. The HEART score divides patients into low (0-3), intermediate (4-6) or high risk groups (7-10), with mean risks of an event of 0.9%, 12% and 65%, respectively. Consequently, an evidence-based decision may be made to discharge the patient from the ED or to admit for clinical observation or immediate aggressive therapies.

In addition, the HEART score is currently being validated in a multicenter prospective study in 2440 patients at 10 hospitals. Follow up will be finalized by the end of the year 2010.

Clinical Practice

Chest pain patients in the ED create uncertainty for all treating physicians. The decision to discharge a patient where ACS cannot be excluded may result in a serious life-threatening outcome, while on the other hand, admission in case of atypical chest pain can lead to unnecessary medical treatment and costs. Risk score models may help the physician in making a timely decision in the emergency setting. In clinical practice, simple risk scores may be favourable, in particular when they can be calculated at the patient's bedside.

For several years, researchers tried to develop a risk score for chest pain patients. Most of these risk scores have turned out to be difficult to use, require the use of a computer and, more importantly, are only validated for a selected group of patients such as STEMI or non-STEMI patients in the coronary care unit. The main purpose of all these risk scores was not to make a diagnosis, but to identify the subset of high risk ACS patients who are likely to benefit most from aggressive therapies.

For NSTE-ACS, several risk scores have been developed and validated in large patient populations. Most useful are the PURSUIT [4], TIMI [5] and GRACE [9,10] risk scores, which were compared by De Araújo Gonçalves [6] and Yan [7]. Despite the firm scientific basis for all three scoring systems and the recommendations in the guidelines, none is widely applied in clinical practice.

There is a clear difference in approach to patients admitted at the coronary care unit and patients presenting to the ED with suspected ACS. In “real life”, as experienced by every physician, the whole range of chest pain patients presenting to the ED runs from atypical chest pain to acute myocardial infarction. Therefore, the ideal risk score is capable of identifying patients at both ends of the spectrum.

Applicability per Score

The PURSUIT study was conducted before the general introduction of the troponin assay. This crucial test, which is now generally applied, was not included in the PURSUIT score. This is one of the reasons why the score has not found its place in routine clinical practice. Another objection is that the PURSUIT score is determined for more than 50% by the age of the patient. Not surprisingly, higher ages of patients accompany higher mortality rates. This knowledge does not help the clinician to make better decisions in the emergency setting. The PURSUIT score has good predictive power for death alone (c-statistic0.84), but rather poor predictive power for the combined endpoint of death/MI (c-statistic 0.67).

The c-statistic of the TIMI score is 0.65 for the combined endpoint, indicating poor predictive power, but its simplicity makes it more useful than other scores. Even though the TIMI score is simple to calculate, it allows only binary choices, thereby ignoring the fact that many variables have “grey levels”.

The GRACE risk score has a good discriminative power with a c-statistic of 0.83. However, the complexity of the system requires special calculating tools to estimate risk at the bedside. Like the PURSUIT score, the GRACE score is determined to a large extent by the age of the patient, an element that holds only indirect evidence of coronary artery disease. Unfortunately, the GRACE investigators do not divide patients into different risk groups, making it less easy for the physician to interpret a patient’s individual score.

The FRISC score is quite comparable to the TIMI score, with a c-statistic of 0.70 for the combined endpoint, indicating only moderate discriminative power. The FRISC score is simple to calculate, but again allows only binary choices.

Furthermore, none of the scores emphasizes the value of patient history, despite the fact that clinicians rely heavily on this aspect. The clinical judgement of the treating physician will already divide patients into low, intermediate and high risk groups for an adverse event. Without doubt, clinicians have developed strong competence in patient selection, not requiring complex algorithms and computer based calculating tools. Therefore, the ideal risk score closely follows this clinical reasoning. Based on general impression, patient history, ECG characteristics, risk factors for coronary atherosclerosis and levels of cardiac markers, a quick estimation can be made of the individual patient's risk.

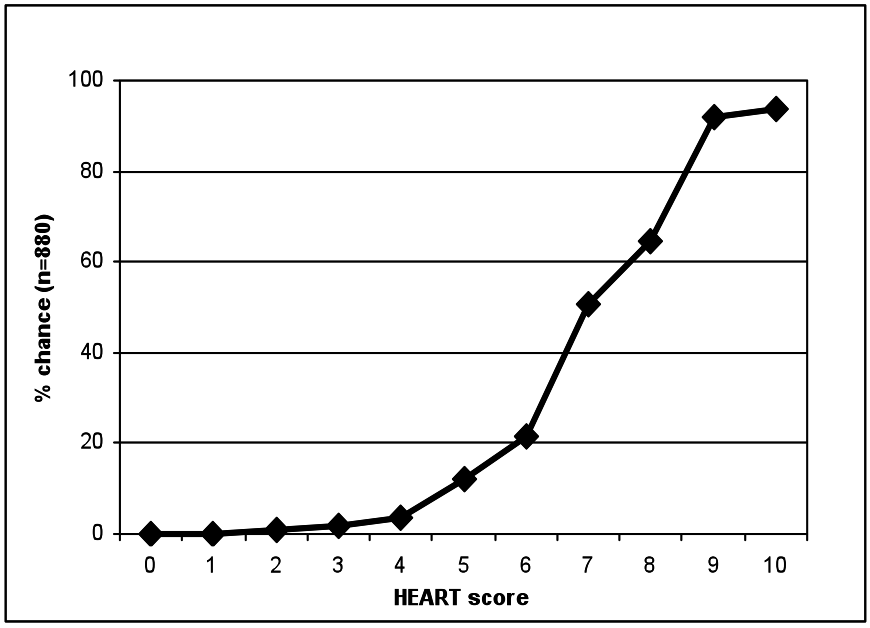
Newly Developed Risk Score

The HEART risk score was specifically developed for chest pain patients presenting to the ED. The HEART score encloses each of the previous mentioned parameters of clinical judgement: History, ECG, Age, Risk factors and Troponin levels. The HEART score translates the clinical judgement into a uniformly comprehensive number of 0-10.

Using the HEART score as guidance in the treatment of chest pain patients will clearly result in benefits for patients on both sides of the spectrum. The risk of MACE in patients with a HEART score ≤ 3 is 0.9%, 12% in patients with HEART score 4-6 and 65% in patients with a HEART score ≥ 7 (Figure 1) [14]. Well known markers of increased risk, such as higher age, presence of risk factors and history of coronary atherosclerosis, are all incorporated in the HEART score. The combination of the five elements will allow for a more firmly based decision, mainly in cases of atypical presentation or absence of ECG abnormalities.

Compared with other risk scores, the HEART score is superior in terms of both simplicity and predictive power, not only for patients at high risk but also those patients at low risk for ACS (Table 6). Therefore it is quite useful for bedside clinical practice.

Figure 1. Probability of reaching a MACE in each HEART category[14].



CONCLUSION

Previously developed risk scores for chest pain patients are designed to identify the subgroup of ACS patients in the CCU who are at the highest risk of an adverse event. Most of the described risk scores were developed after identification of those risk factors which were independently associated with the primary endpoint, usually death and/or MI. Statistically, these scores have a firm basis. However, the selection of parameters and their individual weighting make them less applicable in the bedside setting. The recently developed HEART score for chest pain patients in the ED closely follows clinical reasoning. Therefore, it is far more applicable to the whole range of chest pain in the emergency setting. The HEART score appears a strong predictor of event free survival on one hand and potentially life threatening cardiac events on the other hand. A direct comparison of the various risk scores within one clinical study is desirable.

Table 6. Summary of clinical risk scores for ACS, after Morrow[15].

	PURSUIT		TIMI	GRACE	FRISC		HEART
Population	UA/NSTEMI		UA/NSTEMI	All ACS	UA/NSTEMI		All Chest Pain
Outcome	Death	Death/MI			Death	Death/MI	
Key elements	5		7	8	7		5
Age	X		X	X	X		X
Gender	X				X		
Prior MI/CAD			X		X		X
DM, CRF's			X		X		X
Symptoms/History	X		X				X
Use of aspirin			X				
Weight							
HR				X			
SBP				X			
CHF/Killip class	X			X			
ECG	X		X	X	X		X
CKMB/cTn			X	X	X		X
Serum Cr				X			
Serum Interl-6/CRP				X	X		
Cardiac Arrest							
Possible max score	18		7	372	7		10
c-statistic	0.84	0.67	0.65	0.83	0.77	0.70	0.90
Computer needed				Yes			

PURSUIT = Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy, TIMI = Thrombolysis in Myocardial Infarction, GRACE= Global Registry of Acute Coronary Events, FRISC = Fast Revascularisation in Instability in Coronary disease, HEART = History ECG Age Risk Factors Troponin, UA = Unstable Angina, NSTEMI = Non-ST Elevation Myocardial Infarction, ACS = Acute Coronary Syndrome MI = Myocardial Infarction, CAD = Coronary Artery Disease, DM = Diabetes Mellitus, CRF's = Cardiac Risk Factors, HR = Heart Rate, SBP = Systolic Blood Pressure, CHF = Congestive Heart Failure, ECG = Electrocardiogram, CKMB = Creatininfosfokinase MB, cTn = cardiac Troponin, Serum Cr = Serum Creatinin, Serum Interl-6 = Serum Interleukin-6, CRP = C-Reactive Protein.

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The HEART score validation studies

Part Three
The HEART score sub studies

Part Four
Appendix

Part Five

Chapter 3

Chest pain in the emergency room: value of the HEART score

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ABSTRACT

Background. Chest pain is one of the most common causes of presentation to the emergency room. The diagnosis of non-ST-elevation acute coronary syndrome typically causes uncertainty. Classical considerations for risk stratification are History, ECG, Age, Risk factors and Troponin (HEART). Each can be scored with zero, one or two points, depending on the extent of the abnormality. The HEART score is the sum of these five considerations.

Methods. Clinical data from 122 patients referred to the emergency room for chest pain were analysed. The predictive value of the HEART score for reaching an endpoint was evaluated in 120/122 patients.

Results. Twenty-nine patients reached one or more endpoints: an acute myocardial infarction was diagnosed in 16 patients, 20 underwent revascularisation and two died. The HEART score in the patients with and without an endpoint was 6.51 ± 1.84 and 3.71 ± 1.83 ($p<0.0001$) respectively. A HEART score of 0-3 points holds a risk of 2.5% for an endpoint and supports an immediate discharge. With a risk of 20.3%, a HEART score of 4-6 points implies admission for clinical observation. A HEART score ≥7 points, with a risk of 72.7%, supports early invasive strategies.

Conclusion. The HEART score facilitates accurate diagnostic and therapeutic choices. The HEART score is an easy, quick and reliable predictor of outcome in chest pain patients.

INTRODUCTION

Chest pain is one of the most common reasons for admitting patients to the emergency room. An acute coronary syndrome (ACS) needs to be distinguished from a variety of other cardiac and noncardiac diseases that cause chest pain. In certain cases, a diagnosis can be made quickly, in particular in the case of an acute transmural myocardial infarction.

Non-ST-elevation ACS (nSTE-ACS), previously called 'unstable angina' or 'pending infarction', typically causes uncertainty[1]. This diagnosis can be made quickly in case of concurrent typical changes in the electrocardiogram (ECG) and/or increased levels of myocardial markers in plasma. Absence of such abnormalities, however, does not always exclude an nSTE-ACS. Therefore, excluding the diagnosis of nSTE-ACS is felt to be hard in the early stages of the diagnostic process. It is important to make a quick diagnosis as patients benefit significantly from early treatment[2]. In addition, a 'missed diagnosis' may result in a wrongful discharge and ultimately in out-of- hospital sudden death when unstable angina becomes a myocardial infarction.

Typically, patients are checked by a resident on duty in the emergency room and subsequently discussed with a supervisor. Based on a general impression, patient history, risk factors, ECG and levels of myocardial infarction markers it is decided whether or not to admit the patient for clinical observation. Typically, all patients under suspicion of the diagnosis of nSTE-ACS are treated as such, awaiting confirmation or exclusion of the diagnosis.

Most data on the risk stratification of nSTE-ACS have been retrieved from clinical drug trials. In these trials, patients were selected with chest pain plus some objective confirmation of the diagnosis. In order to obtain good trial results, low-risk cases were excluded. Therefore, little is known about the natural course of such doubtful cases[3]. How often do we miss the diagnosis of nSTE-ACS in patients with nonspecific chest pain, resulting in a seriously adverse outcome?

As a first step in developing a method for risk stratification, all patients admitted to the emergency room for chest pain during a three-month period were analysed in order to answer two questions: what made doctors decide to admit patients to the

coronary care unit or not, and which were the predictors of acute myocardial infarction, need for revascularisation and death.

METHODS

This study was performed at a 265-bed community hospital. Inclusion criteria for this study were any patient admitted to the emergency room due to chest pain irrespective of age, prehospital assumptions and previous medical treatments. One very relevant population with chest pain that never arrived at the emergency room needs to be mentioned. Patients with chest pain and significant ST-segment elevation on the ECG during transportation in the ambulance were immediately taken to the coronary intervention room in another hospital nearby. Therefore, patients with ST-elevation acute myocardial infarction (STEMI) were not part of the study.

All admission and follow-up data were retrieved from the hospital charts. If follow-up data were lacking, patients were called at home to check their condition.

Expected predictors

Based on clinical experience and current medical literature, we expected specific patient history, ECG abnormalities, higher age, multiple risk factors for coronary artery disease and elevated troponin levels to be predictors of primary endpoints.

Scoring of predictors

History. For the purpose of this study, patient history was classified by two investigators, based on the narrative in the hospital charts written in the emergency room and not allowing for risk factors, ECGs, laboratory results and later developments. In the absence of specific elements in terms of pattern of the chest pain, onset and duration, relation with exercise, stress or cold, localisation, concomitant symptoms and the reaction to sublingual nitrates, the history was classified as 'nonspecific' and granted zero points. If the patient history contained both nonspecific and suspicious elements, the history was classified as 'moderately suspicious' and granted one point. If the history contained primarily specific elements, the history was classified highly suspicious and granted two points.

ECG. The ECG taken in the emergency room was reviewed and classified. If the ECG was 'normal' according to Minnesota criteria[4], zero points were given. In case of repolarisation abnormalities without significant ST-segment depression, one point was given. One point was also granted for bundle branch block, typical abnormalities indicative of left ventricular hypertrophy, repolarisation abnormalities probably due to the use of digoxin or in case of unchanged known repolarisation disturbances. For significant ST-segment depressions or elevations in the absence of a bundle branch block, left ventricular hypertrophy or the use of digoxin two points were given.

Age. For age at the time of admission zero points were given if the patient were younger than 45 years, one point if the patient was between 45 and 65 years and two points if the patient was 65 years or older.

Risk factors. The number of risk factors for coronary artery disease present in the individual were counted. The following risk factors were taken into account: currently treated diabetes mellitus, current or recent (<one month) smoker, diagnosed hypertension, diagnosed hypercholesterolaemia, family history of coronary artery disease and obesity. If the patient had no risk factors at all, zero points were given. For one or two risk factors, one point was given. For three or more risk factors, two points were given. Two points were also given for a history of coronary revascularisation, myocardial infarction, stroke or peripheral arterial disease.

Troponin I. Troponin I levels were measured as Access AccuTroponin I assay. If the troponin I level on admission was below the threshold value for positivity (troponin I ≤0.04) zero points were given. If the level was between once and twice the threshold value for positivity, one point was given. If the level was higher than twice the threshold value for positivity, two points were given.

HEART

The total number of points for History, ECG, Age, Risk factors and Troponin was noted as the HEART score. A grid for the score is given in table 1.

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Endpoints

Endpoints in this study were acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) and death plus a combined endpoint of AMI, PCI, CABG and death.

Statistics

Statistical analysis was performed according to the SAS system (SAS inc, Cary, NC). Descriptive statistics were given as average ± SD, percentage or Kaplan-Meier cumulative event-free curve. Differences between groups were assessed by means of the Student's t-test when normally distributed, for count data we used the Fisher's exact test or in case of ordinal data the Cochran-Armitage trend test. The probability of reaching an endpoint was calculated as the percentage of cases with an endpoint within a category. Statistical significance was defined as $p<0.05$ two-sided.

RESULTS

During the study period, from 1 January to 31 March 2006, a total of 122 chest pain patients were admitted to the emergency room. Patients were 61.2±15.4 years of age. The male/female distribution was 73/49. Race was not routinely noted in the patient charts; in the geographical area of the hospital the vast majority (>95%) of the population were white/Caucasian.

Follow-up

In 120/122 patients (98.3%) long-term follow-up data are available, with a duration of 423±106 days. In two cases follow-up is lacking. These were foreign visitors, one a 42-year-old female from Poland (patient # 47) and one a 30-year-old male from South Africa (patient # 119). Both suffered from nonspecific chest pain and had no abnormalities in their ECG or troponin levels. The HEART scores for these patients were 1 and 0 respectively. Neither were hospitalised. They appear to have returned to their home countries without leaving any traces. Their data are not part of the study's group comparisons.

Endpoints reached

A total of 29 patients (24.1%) reached one or more endpoints. An AMI was diagnosed in 16 patients (13.3%), 14 patients (11.6%) underwent percutaneous coronary intervention (PCI), six (5.0%) had coronary artery bypass graft (CABG) surgery and two (1.6%) died. All endpoints occurred within a time frame of three months.

Myocardial infarction

An AMI was diagnosed in 16 of the 120 patients (13.3%). Fourteen of these patients (87.5%) already had elevated myocardial markers on admission (apparently these AMIs had started before their arrival to the emergency room.) One AMI occurred two days after admission despite medical treatment in a 64-year- old male (# 89). One AMI occurred ten days afterwards in a discharged patient (# 25). This patient is still alive.

Revascularisation

Coronary angiography was performed in 27 of the 120 patients (22.5%). Revascularisation was performed in 20 patients (16.6%): 14 PCIs (11.6%) and six CABGs (5.0%). Of the 77

patients who were hospitalised, 12 (15.5%) had a PCI and six (7.7%) a CABG. In the 43 discharged patients revascularisation was performed in two cases (4.6%). Both were successful single-vessle PCIs, without any complications. This concerns # 25 and # 45.

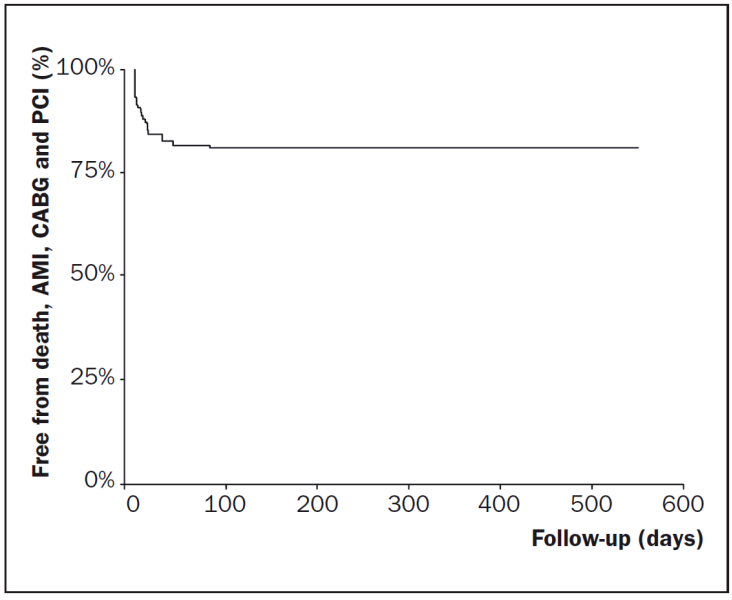
Mortality

Two patients died from the entire study population (1.6%), and death occurred exclusively in the admitted patient group. Both patients were 78-year-old males. One patient died 14 days after admission and the other after 11 days. Both had a HEART score of 8.

Time frame of endpoints

The graph for survival free of acute myocardial infarction and revascularisation is given in figure 1. All endpoints occurred within a time frame of three months.

Figure 1. Acute myocardial infarction, PCI and CABG free survival.



Risk factors for reaching an endpoint

A comparison of the risk profile was made between the patient groups with and without an endpoint. Results are

presented in table 2. Of these variables, a history of hypertension, positive family history and history of peripheral arterial disease were independent predictors of the combined endpoint.

Table 2. Risk profile of patients with and without the combined endpoint of AMI, revascularisation or death.

Variable	Endpoint No	Endpoint Yes	Total	P value
N	91	29	120	
Age	60.5 ± 15.7	64.7± 13.2	61.2 ± 15.4	0.1783
Male gender	50 (54.9%)	22 (75.8%)	72 (60.0%)	0.0522
Diabetes Mellitus	17 (18.6%)	5 (17.2%)	22 (18.3%)	1.0000
Current smoker	26 (28.5%)	10 (34.4%)	36 (30.0%)	0.6425
Hypercholesterolemia	40 (43.9%)	12 (41.3%)	52 (43.3%)	0.8332
Hypertension	29 (31.8%)	18 (62.7%)	47 (39.1%)	0.0048
Family history of coronary artery disease	27 (29.6%)	15 (51.%)	42 (35.0%)	0.0435
Reported obesity	14 (15.3%)	5 (17.2%)	19 (15.8%)	0.7768
History of myocardial infarction	13 (14.2%)	5 (17.2%)	18 (15.0%)	0.6979
History of CABG	3 (3.3%)	0 (0.0%)	3 (2.5%)	1.0000
History of PCI	9 (9.8%)	1 (3.4%)	10 (8.3%)	0.4479
History of stroke	7 (7.6%)	5 (17.2%)	12 (10.0%)	0.1592
History of peripheral arterial disease	1 (1.1%)	3 (10.3%)	4 (3.3%)	0.0434
Use of Aspirin	28 (30.7%)	10 (34.4%)	38 (31.6%)	0.7081
Use of Statins	31 (34.0%)	10 (34.4%)	41 (34.1%)	1.0000

The relation between the five predefined elements of the HEART score for chest pain patients and the occurrence of endpoints is given in table 3. Patient history, ECG abnormalities and elevated troponin values were independent predictors of the combined endpoint. The average HEART score in the no endpoint group was 3.71±1.83 and in the patients with at least one endpoint 6.51±1.84 ($p<0.0001$).

Table 3. Numbers of patients in each element of the HEART score in groups with or without endpoints.

	No end point reached n = 91			**One or more endpoints reached** n = 29			P value
Points	**0**	**1**	**2**	**0**	**1**	**2**	
History	44	37	10	5	10	14	<0.0001
ECG	60	23	8	8	4	17	<0.0001
Age	13	36	42	4	7	18	0.2847
Risk factors	15	44	32	3	9	17	0.0827
Troponin	82	4	5	15	1	13	<0.0001
HEART score (Average +/- SD)	3.71+/- 1.83			6.51 +/- 1.84			<0.0001

Distribution

The distribution of HEART scores in patients with or without the combined endpoint of AMI, revascularisation or death is given in figure 2. The HEART score follows Gaussian distribution in both groups.

The HEART score yields all crucial information that can correctly place patients into low-, intermediate- and high-risk groups for clinically important irreversible adverse cardiac events: myocardial infarction, revascularisation and cardiac death. One of the 39 patients (2.5%) with a HEART score of 0-3 points had an endpoint. This was a patient who required a CABG 11 days after admission. In the 59 patients with a HEART score of 4-6 points, 12 (20.3%) had an endpoint. In case of a HEART score of 7-10 points, 16 of 22 (72.7%) reached the combined endpoint. In addition, figure 3 illustrates an almost linear relation between the HEART score and the chance of reaching an endpoint (p for trend <0.001).

Figure 2. Percentages of patients in each HEART score in groups with and without the combined endpoint of AMI, revascularisation or death (MACE).

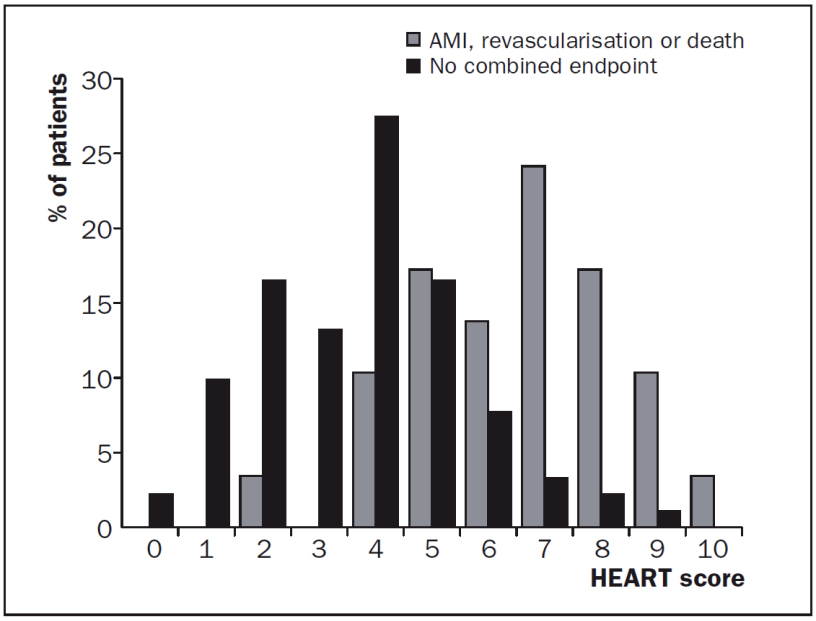
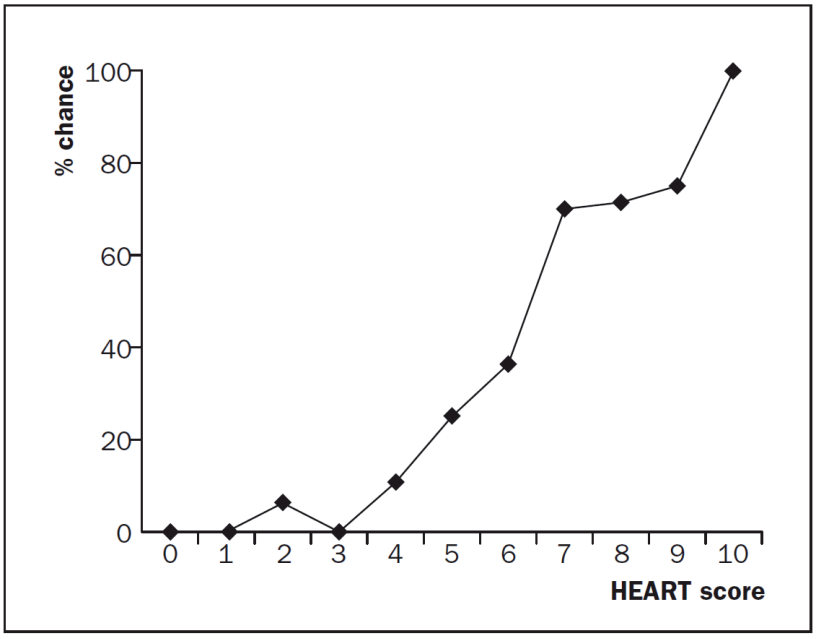


Figure 3. Chances of reaching a MACE in each HEART category.



DISCUSSION

Definition of ACS

Chest pain patients in the emergency ward create uncertainty for all treating physicians, in particular when no diagnosis is made. The diagnosis of nSTE-ACS may be easy to confirm but is often hard to exclude[5].

Corroboration of this article may be found in the inclusion criteria for the major treatment trials in ACS, where patients were randomised only when the diagnosis was confirmed by means of typical ECG changes and/or elevated troponin levels. Unconfirmed cases of ACS were ignored in such trials. Although the landmark drug trials have provided a wealth of data on the natural course of high risk nSTE-ACS and have proven the (lack of) efficacy of various treatments, the optimal approach for patients with borderline evidence of an nSTE-ACS is largely unknown. This is also reflected in the current American and European guidelines[6,7].

HEART score

Challenged by the lack of exact definitions or criteria for nSTE-ACS, we attempted to define an easy-to-use policy for clinicians. The starting-point question was: which are the decisive factors in practice? They are History, ECG, Age, Risk factors and Troponin. Similar to the Apgar score[8], globally used to assess the need for intensive care in newborns, these five factors can be fused together. Each of the five factors can be appreciated with 0, 1 or 2 points. The sum of all five is called the HEART risk score for chest pain patients.

Definitions were based on literature as much as possible. Continuous variables such as age and troponin are exactly defined. Unfortunately, definitions for patient history are lacking in the literature. Therefore, patient history is subject to personal interpretations. Our experience is that the HEART score for individual patients can be calculated without a calculator and even without a sheet of paper.

Literature

In the literature, several risk scores for nSTE-ACS have been published. The most reputed are the TIMI[9],

PURSUIT[10] and GRACE[11,12] risk scores, which were compared by De Araújo Gonçalves[13]. Despite the firm scientific basis for all three scoring systems and the recommendations in guidelines, none is widely applied in clinical practice. These classical scoring systems do not show much interest in the differentiation of chest pain patients who are at low to moderate risk for an adverse outcome. The TIMI and PURSUIT scores were designed to identify high-risk patients, who are most likely to benefit from aggressive therapy. The major disadvantage of the GRACE score is that it can only be calculated with the use of the internet. The TIMI score is simple to calculate, but it is quite rough as it allows only binary choices, thus ignoring the fact that many variables have a 'grey area'. The PURSUIT score is outdated as it was designed before the introduction of troponin assays for clinical use.

Advantages

A major advantage of the HEART score is that it facilitates communication between doctors. A single figure summarises at least ten lines of descriptions and considerations about chest pain patients. For example, when the resident calls the supervisor to discuss the use of limited resources for two chest pain patients, one with eight points and another with two points, choices may appear clear.

Guidelines could be easily and briefly formulated when based on the HEART score. A score of 0-3 points holds a risk of 2.5% of reaching an endpoint and therefore supports a policy of early discharge. With this very low risk percentage in mind, it is doubtful whether additional diagnostic procedures at the outpatient clinic will be useful. With a HEART score of 4-6 points, immediate discharge is not an option as this figure indicates a risk of 20.3% for an adverse outcome. These patients should be admitted for clinical observation, treated as an ACS awaiting final diagnosis and subjected to noninvasive investigations, such as repeated troponin, exercise testing and possibly advanced ischaemia detection. A HEART score ≥7 points, with a risk of 72.7%, implies early aggressive treatment including invasive strategies without preceding noninvasive testing. Clearly, cut-off points may need to be validated in larger multicentre studies.

Limitations

Our study is a careful scientific analysis of a clinical view. Some people believe that only prospective, randomised studies hold true. Our study was set up as a pilot study and was observational and retrospective for the simple reason that this is the optimal design to answer the questions of the study, without the other- wise unavoidable risk of influencing the outcome by the experimental setting. However, we believe that the unexpected significance of the study provides a firm basis for further investigation.

CONCLUSIONS

The HEART score helps the cardiologist in making accurate diagnostic and therapeutic choices in a setting that is currently denoted by uncertainty and a lack of guidance by the medical literature. The HEART score is an easy, quick and reliable predictor of outcome in chest pain patients and can therefore be used for triage.

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Chapter 4

Chest pain in the emergency room a multicenter validation of the HEART score

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***Crit Pathways in Cardiol* 2010;9: 164 –169**

ABSTRACT

Objective: Decision-making in chest pain patients is hampered by poor diagnostic power of patient's history, electrocardiogram, age, risk factors, and troponin. Each of these findings may be qualified with 0, 1, or 2 points. Together they compose the HEART score. We tested the hypothesis that the HEART score predicts major adverse cardiac events.
Design: Retrospective multicenter analysis in patients presenting at the cardiology emergency room.
Setting: Patient inclusion between January 1 and March 31, 2006.
Patients: A total of 2161 patients were admitted, of which 910 patients (42%) presented with chest pain. Analysis was performed in 880 cases (96.7%).
Main Outcome Measures: The primary endpoint was a composite of acute myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery and death, within 6 weeks after presentation, together called major adverse cardiac events.
Results: A total of 158 patients (17.95%) reached the primary endpoint. Ninety-two patients had an acute myocardial infarction (10.45%), 82 a percutaneous coronary intervention (9.32%), 36 a coronary artery bypass graft (4.09%), and 13 died (1.48%). Of 303 patients with HEART score 0 to 3, three (0.99%) had an endpoint. In 413 patients with HEART score 4 to 6, 48 cases (11.6%) reached an endpoint. In case of a HEART score of 7 to 10, an endpoint was reached in 107/164 cases (65.2%).
Conclusions: The HEART score helps in making accurate diagnostic and therapeutic decisions without the use of radiation or invasive procedures. The HEART score is an easy, quick, and reliable predictor of outcome in chest pain patients and can be used for triage.

INTRODUCTION

Chest pain is one of the most common reasons for which patients are admitted to the emergency room. A differential diagnosis must be made between an acute coronary syndrome (ACS) and other diagnoses. The diagnosis of non-ST-elevation-ACS (nSTE-ACS), often called unstable angina or pending infarction, typically causes uncertainty as this is not a strictly defined, exclusive diagnosis[1-3].

Individual considerations are made in each patient. Various relative arguments play a role. A suspicious patient history may be reason enough to consider the diagnosis, but typically it is supported by other diagnostic elements such as electrocardiogram (ECG) abnormalities, advanced age, risk profile, and/or increased troponin levels. Each of these findings may be a separate, convincing argument for the diagnosis of ACS.

With this in mind, various parameters were combined into the HEART score. The acronym is an abbreviation of the words: History, ECG, Age, Risk factors, and Troponin. Each of these may be qualified with 0, 1, or 2 points. The composition of the HEART score is shown in Table 1.

In a pilot study of 122 patients, conducted at a single site, we tested the hypothesis that the HEART score predicts the short-term occurrence of myocardial infarction, revascularization, and death[4].

These outcomes are all adverse events typically related to an ACS, and therefore considered indirect proof of the diagnosis. The results were favorable. A HEART score ≤ 3 implied a chance of only 2.5% for reaching the end point, whereas in patients with a HEART score ≥ 7 this chance was 72.7%. As a result of these findings, we believed that this score was of potential use when making treatment decisions in chest pain patients in the emergency room. To confirm the findings of the pilot study and to validate the HEART score in various subgroups, we conducted a new retrospective study at 4 sites. In summary, we investigated the predictive value of early clinical findings for the final outcome.

METHODS

This study was performed at 4 separate hospitals in the Netherlands. Three sites were community-based hospitals with 262 beds (Zuwe Hofpoort Ziekenhuis, Woerden, The Netherlands), 529 beds (MESOS, Utrecht, The Netherlands), and 881 beds (Reinier de Graaf Groep, Delft, The Netherlands) and one was an academic hospital (University Medical Center, Utrecht, The Netherlands) with 1042 beds.

Inclusion Criteria

This study included any patient admitted to the (cardiology) emergency room because of chest pain irrespective of age; prehospital assumptions; and previous medical treatment. In most cases, patients with chest pain and significant ST- segment elevations on the ECG during transportation in the ambulance were immediately taken to a coronary intervention room elsewhere. Consequently, most patients with ST-elevation myocardial infarction were not enrolled in the study.

Data Acquisition

All admission data were retrieved from the hospital charts of the study patients. The same applies to follow-up data. In case there was no follow-up, either the patients or their General Practitioners were called to inform about their condition and check for possible hospital admissions, myocardial infarction, and revascularization at other medical centers.

Scoring of Predictors

History: For the purpose of this study, patient history was classified by at least 2 investigators on the basis of narration in the hospital charts in the emergency room, without regard for risk factors, ECGs, laboratory results, and later developments. In absence of specific elements in the patient history for coronary ischemia, the history was classified as nonspecific and granted 0 points. In case the patient history contained both nonspecific and suspicious elements, the history was classified moderately suspicious and

assigned 1 point. In case the history contained mainly suspicious elements, such as middle- or left-sided, heavy chest pain, radiation, and/or relief of symptoms by sublingual nitrates, the history was classified highly suspicious and granted 2 points.

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

***Electrocardiogram*:** The ECG taken at the emergency room was reviewed and scored by 2 cardiologists. In case of a normal ECG according to Minnesota criteria[5], 0 points were given. In case of repolarization abnormalities without significant ST-segment depression or elevation, 1 point was given. Also in case of the presence of a bundle branch block or pacemaker rhythm, typical abnormalities indicative of left ventricular hypertrophy, repolarization abnormalities probably caused by digoxin use, or in case of unchanged known repolarization disturbances, 1 point was given. In case of significant ST- segment depressions or elevations in absence of a bundle branch block, left ventricular

hypertrophy, or the use of digoxin, 2 points were given.
In case there was disagreement in the scoring of History and/or ECG, a third opinion was taken to reach a conclusion.
Age: Zero points were given if the patient was younger than 45 years at the time of admission, 1 point if the patient was 45 to 65 years, and 2 points if the patient was 65 years or older.
Risk Factors: The number of risk factors for coronary artery disease present in the individual was counted. The following risk factors were taken into account: currently treated diabetes mellitus, current or recent (< 90 days) smoker, diagnosed and/or treated hypertension, diagnosed hypercholesterolemia, family history of coronary artery disease, obesity (body mass index BMI 30), or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke, or peripheral arterial disease, irrespective of the risk factors for coronary artery disease). If the patient had no risk factors at all, 0 points were given. If the patient had 1 or 2 risk factors, 1 point was given. Two points were given if the patient had 3 or more risk factors, and also if the patient had a history of significant atherosclerosis.
***Troponin*:** Troponin T or I levels were measured according to local laboratory standards. If the Troponin T or I level on admission was below the threshold for positivity, 0 points were given. If the level was between 1 and 3 times the threshold for positivity, 1 point was given. If the level was higher than 3 times the threshold for positivity, 2 points were given.

Other Definitions

Percutaneous coronary intervention (PCI) was defined as any therapeutic catheter intervention in the coronary arteries. Coronary artery bypass graft (CABG) was defined as any cardiac surgery in which coronary arteries were operated.

An acute myocardial infarction (AMI) was defined as a syndrome consisting of typical chest pain, ECG changes, and rise of creatine phosphokinase and troponin serum levels. In case 1 of the 4 elements was absent or nonevaluable (eg, patients without chest pain or with a bundle branch block), the case was discussed in the adjudication committee.

Primary Endpoints

The primary end point in this study was a composite of: AMI, PCI, CABG surgery, and death, all occurring within 6 weeks, together called major adverse cardiac events (MACE). These outcomes are typically related to an ACS, and therefore considered indirect proof of the diagnosis.
In the pilot study with 122 patients, all end points occurred within 3 months. Most occurred within 6 weeks[4]. MACE occurring within 6 weeks after an ACS were likely to be the result of the index ACS. In case of a MACE after 6 weeks, the causal connection becomes less evident. Therefore, a window of 6 weeks was chosen for the primary end point.

Secondary Endpoints

Secondary endpoints were MACE after 6 weeks and coronary angiography.

Statistics

Statistical analysis was performed with R (Version 2.9; The R foundation for Statistical Computing, Vienna, Austria)[6]. Descriptive statistics are given as average Standard deviation (SD), percentage, or Kaplan-Meier cumulative event-free curve. Differences between groups were assessed by means of the Student *t* test when normally distributed; for scalar data we used the Fisher exact test or in case of ordinal data the Cochran-Armitage Trend Test. The probability of reaching an end point was calculated as the percentage of cases with an end point within a category. The area under the receiver-operator characteristic curve (c-statistic) was computed to give a measure of diagnostic discriminative strength, combining sensitivity and specificity, especially for nonbinomial variables. Statistical significance was defined as $p \leq 0.05$, 2-sided.

RESULTS

During the study period, which lasted from January 1 to March 31 2006, a total of 2161 patients were admitted to the (cardiac) emergency rooms of the participating sites. Race was not routinely noted in the patient charts; in the geographic area of the hospitals the population is predominantly Caucasian. Data

retrieved from hospital charts were almost complete, except from notes on the absence or presence of obesity, which were missing in a majority of cases. In case obesity was not mentioned, it was assumed the patient was unlikely to be morbidly obese.

The main reasons for admission to the cardiac emergency room included chest pain (42.1%), palpitations or rhythm disturbances (16.8%), dyspnea or heart failure (13.4%), syncope (9.3%), or other/noncardiac complaints (18.2%). Chest pain was the main reason for admission in 910 patients (42.1%) (Figure 1). Thirty cases (3.3%) were nonevaluable as the follow-up data were too limited. The group of excluded patients consisted mainly of young men (mean age, 44 ± 20) and had a mean HEART score of 2.1 ± 1.6. The study group consisted of the remaining 880 patients. Mean age was 61.9 ± 15.7 years. The male/female distribution was 500/380. Patient characteristics are presented in Table 2.

Figure 1. MACE indicates major adverse cardiac events; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

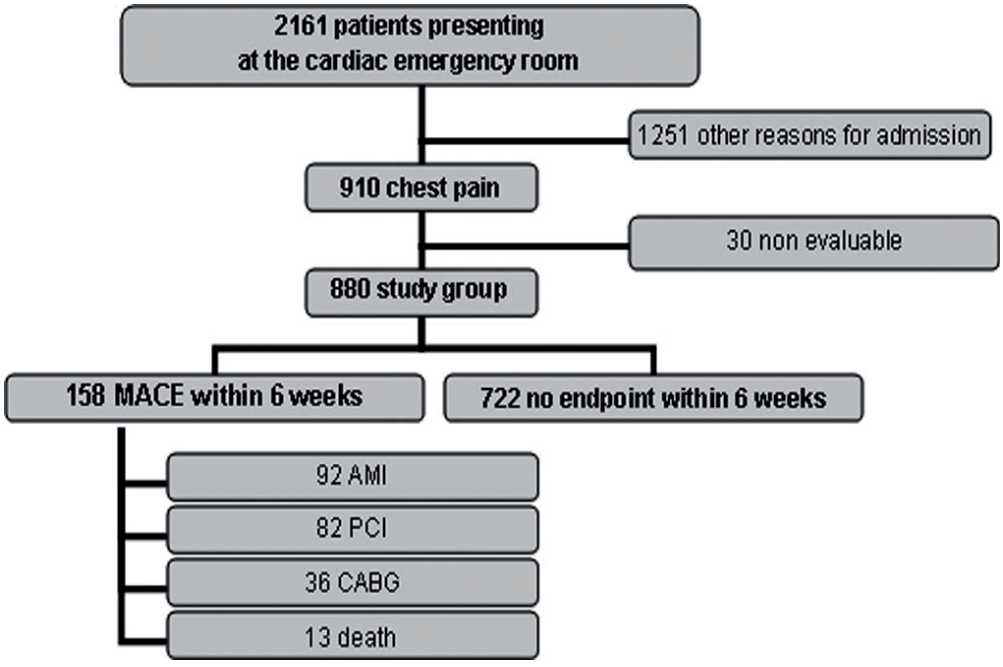


Table 2. Patient characteristics

	N	%
Age (mean (sd))	61.3	(15.7)
Male gender	521	57.3
Diabetes Mellitus	175	19.9
Smoking	257	29.2
Hypercholesterolemia	229	26.0
Hypertension	321	36.5
Family History	281	31.9
Systolic blood pressure (mean (sd))	148.1	(26.5)
Diastolic blood pressure (mean (sd))	83.8	(14.9)
History of AMI	180	20.5
History of CABG	73	8.3
History of PCI	118	13.4
History of Stroke	85	9.7
History of peripheral arterial disease	47	5.2
Salicylates	319	36.2
HEART score (mean (sd))	4.51	(2.24)

AMI = Acute Myocardial Infarction. PCI = Percutaneous Coronary Intervention. CABG = Coronary Artery Bypass Graft.

Follow-up

In 880 patients (96.7%), long term follow-up data are available, with total duration of 1681 patient years and a mean duration of 697 ± 265 days. As mentioned earlier, follow-up in 30 cases is absent. Their data are not part of the group comparisons of the study.

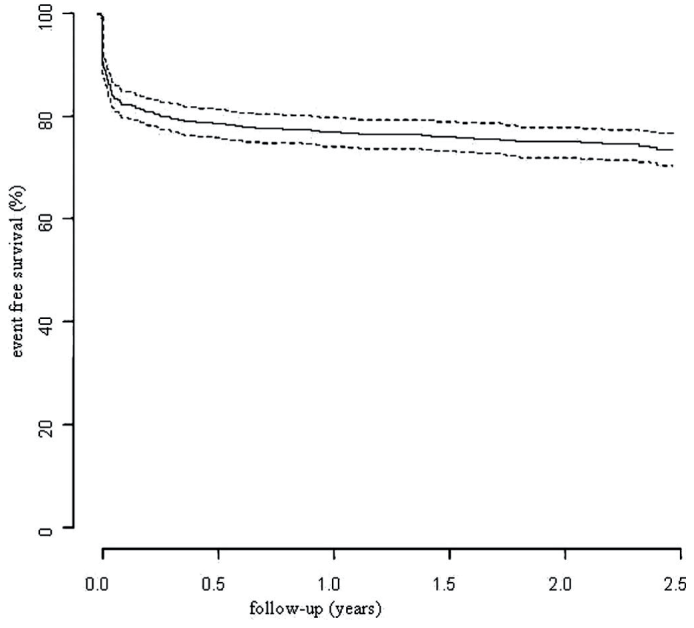
Primary Endpoints

A total of 158 patients (17.95%) had a MACE within 6 weeks: an AMI was diagnosed in 92 patients (10.45%), 82 patients (9.32%) underwent PCI, and 36 patients (4.09%) had CABG. One patient underwent both PCI and CABG. The mortality was 13 (1.48%). Altogether, 223 major events occurred in 158 patients, an average of 1.4 events/MACE patient.

Time frame of endpoints

The graph for survival without AMI and revascularization is displayed in Figure 2.

Figure 2. Patients free from death, acute myocardial infarction, PCI, and CABG. Kaplan-Meier curve with 95% confidence interval.



Risk factors leading to MACE

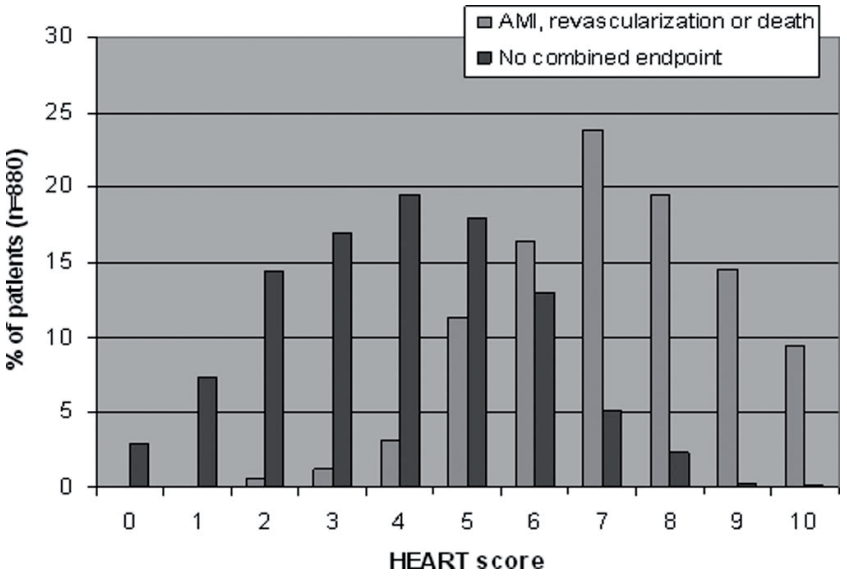
A comparison was made of the risk profile in patient groups with and without a MACE. Independent predictors of MACE included age ($p \leq 0.0035$), male gender ($p \leq 0.0001$), diabetes mellitus ($P \leq 0.0181$), hypertension ($p \leq 0.0474$), history of myocardial infarction (p 0.0149), use of aspirin (p 0.0369), and the HEART score ($p \leq 0.0001$).

The 5 predefined elements of the HEART score for chest pain patients and the occurrence of end points were evaluated. History, ECG, and troponin were independent predictors of the combined end point ($p \leq 0.0001$). The average HEART score in the no end point group was 3.8 ± 1.9 and in the patients with at least one end point was 7.2 ± 1.7 ($p \leq 0.0001$). The c-statistic for the HEART score was 0.897, which indicates a good to excellent ability to discriminate.

Distribution

The distribution of HEART scores in patients with or without the combined end point of AMI, revascularization, or death is shown in Figure 3. The HEART score follows Gaussian distribution in both groups.

Figure 3. Percentage of patients in each HEART score in groups without (darker bar) and with (lighter bar) the combined endpoint of AMI, revascularization or death.



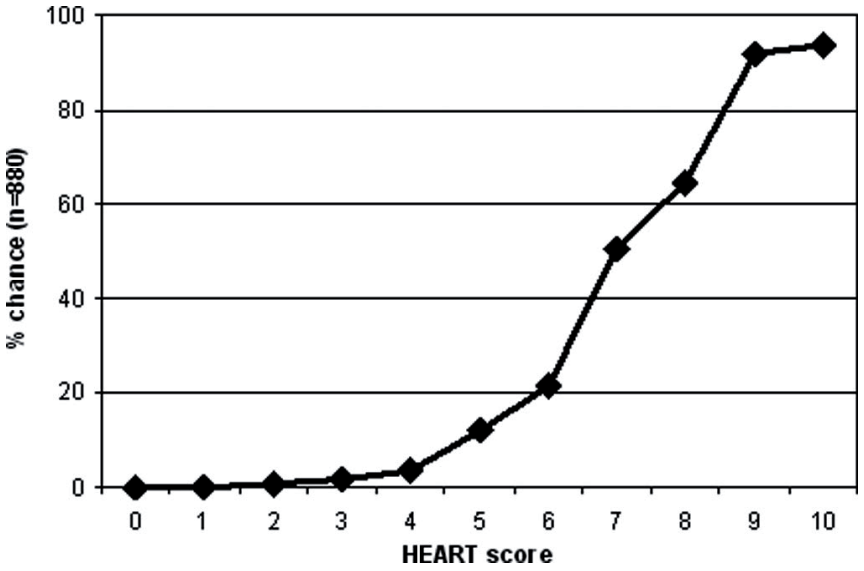
HEART Score at the ER

The HEART score helps to stratify chest pain patients in the emergency room into low, intermediate, and high likelihood groups for clinically important irreversible adverse cardiac events. Three of the 303 patients (0.99%) with

HEART score between 0 and 3 points had a MACE. Of the 413 patients with HEART score between 4 and 6 points 48 (11.6%) had a MACE. In case of a HEART score of 7 to 10 points, 107 of 164 patients (65.2%) had a MACE.

Figure 4 illustrates an almost perfect S-shape relation between the HEART score and the probability of reaching an end point ($p \leq$ for trend 0.001). The relation was close to linear between HEART scores 3 to 9.

Figure 4. Probability of reaching a MACE in each HEART category.



Secondary endpoints

MACE after 6 weeks and within the first year occurred in 54 patients: 5 had an AMI, 19 had a PCI, 11 had a CABG, and 24 patients died. The HEART score was 4.5 ± 2.2 in the group with no MACE after 6 weeks and within the first year, and 6.3 ± 1.8 in the group with MACE after 6 weeks and within the first year.

Kaplan-Meier estimates of the coronary angiography rate within the first 6 weeks was 17.8% and within the first year 23.0%. The HEART score was 3.8 ± 1.9 in the group with no catheterization in the first 6 weeks and 6.9 ± 1.8 in the group

with a catheterization in the first 6 weeks ($p \leq 0.001$).

Subgroups

We have computed the c-statistic of the HEART score in 3 relevant subgroups with regard to the diagnosis of acute coronary syndromes. In patients with diabetes, the event rate was 38/175 and the HEART score retained its discriminative ability, with the c-statistic being 0.909. In women (event rate 41/380) the c-statistic was also 0.909. In the elderly over the age of 80 years (event rate 19/110), the c-statistic was 0.872.

DISCUSSION

Definition of acute coronary syndrome

Chest pain patients at the emergency ward create uncertainty for treating physicians. The decision to discharge a patient without a diagnosis causes insecurity. A missed diagnosis may soon result in a seriously life-threatening outcome, whereas unnecessary hospital admissions may result in overtreatment, with all possible side-effect and higher medical cost.

The diagnosis of nSTE-ACS, often called unstable angina, may be easy to confirm but is often hard to rule out. This thesis is illustrated by the inclusion criteria for the major treatment trials in unstable angina or ACS, where patients were randomized only after a confirmed diagnosis by means of typical ECG changes and/or elevated troponin levels. Unconfirmed cases of ACS were excluded in such trials despite the real possibility that in fact such chest pain patients, without additional abnormalities, did suffer from ACS. Surprisingly, one of the most common diagnoses in hospital medicine has neither absolute nor widely accepted criteria. This is also reflected in the current American and European guidelines[7,8].

HEART Score

Challenged by a lack of exact definitions or criteria for nSTE-ACS, we attempted to define an easy-to-use, common sense- based policy for both junior and senior clinicians. The

starting question was as follows: What, in practice, are the important decision-making factors? These are History, ECG, Age, Risk factors, and Troponin. Similar to the Apgar score[9], which is used world-wide to stratify newborns in low- and high-risk categories, these 5 factors can be combined into the HEART score for chest pain patients. Our experience is that the HEART score for individual patients can be calculated without a calculator, or even pen and paper, by everyone from a young resident to an experienced cardiologist.

Unfortunately, a gold standard for nSTE-ACS is lacking. Therefore, we calculated the relation between HEART scores and the occurrence of adverse outcomes, which is by nature a heavy underestimation of the occurrence of nSTE-ACS. In absence of strict definitions of ACS, we used MACE as the primary end point. As shown in Figure 4, the relation between the HEART score and the occurrence of MACE within 6 weeks is reflected by a nearly perfect S-shaped curve. This enables the assessment of an individual patient's chances.

Elements of the HEART Score

Each of the HEART score elements has a certain predictive value toward the occurrence of end points. Every clinician knows from experience that he or she can rely to some extent on a carefully taken history. Unfortunately, previously developed risk scores, such as the PURSUIT[10], GRACE[11,12], and TIMI[13] scores, did not classify the patient history. The HEART study classified a patient's history numerically. A nonsuspicious patient history (H 0) has a negative predictive value of 95.8% (296/309), whereas a suspicious patient history (H 2) goes with a positive predictive value of only 44.4% (107/241). The value of History is similar to the elements ECG, age, and risk factors in the sense of high-sensitivity counter- balances by low-specificity. In contrast, troponin has a high specificity. However, the single troponin measurement on admission lacks the necessary sensitivity to function as a sole basis for taking clinical decisions.

HEART versus other scoring methods

Several other risk scores for ACS have been published. Most highly regarded are the PURSUIT[10], GRACE[11,12] and

TIMI[13] scores, which were compared by De Araújo Gonçalves et al[14] and Yan et al[15]. Despite the firm scientific foundations and the guideline recommendations of these 3 scoring systems, none is widely applied in clinical practice. These scoring systems focus primarily on recognizing high-risk patients in a hospitalized population and show less of an interest in differentiation within most of low-risk patients. None of the 3 appreciates the value of patient history, despite the fact that clinicians rely so heavily on this aspect. The GRACE score is based on large population studies. A disadvantage is that in practice it can only be calculated with the use of a computer. Another objection is that the GRACE score is determined to a large extent by the age of the patient. Not surprisingly, higher ages accompany higher mortality rates. The TIMI score allows only binary scores, thereby ignoring the fact that many variables have a "gray area." Finally, the PURSUIT score is outdated; it was designed before the introduction of the troponin measurement for clinical use, and therefore not found its place in clinical practice.

Clinical Consequences

A major advantage of the HEART score is that it facilitates communications between doctors. A single figure summarizes extensive descriptions and considerations about chest pain patients. A score of 0 to 3 points carries a risk of 0.99% for reaching a MACE, and therefore supports a policy of early discharge. With this very low-risk percentage in mind, it is doubtful whether additional diagnostic procedures at the outpatient clinic are useful.

In case of a HEART score of 4 to 6 points, immediate discharge is not an option, as this figure indicates a risk of 11.6% for a MACE within 6 weeks. Such patients should be admitted for clinical observation, treated as an ACS awaiting final diagnosis, and subjected to noninvasive investigations such as repeated Troponin, exercise testing, and possibly advanced ischemia detection.

A HEART score ≥ 7 points, with a risk of 65.2% for a MACE, calls for early aggressive treatments possibly including invasive strategies without preceding noninvasive testing.

Limitations

The advantage of our retrospective approach is that this enabled us to analyze complete series of consecutive patients. Consequently, this study is not hampered by the selection bias that is often so harmful for prospective studies. The disadvantage of a retrospective study, namely possible interpretation bias, was kept minimal by the interpretation of separated data regarding patient history, ECG, and outcome by experienced cardiologists.

Our study was observational and retrospective for the simple reason that this was the most pragmatic and practical condition to answer the questions at hand. We believe that the study's unexpectedly high level of significance provides a firm basis for further research. Clearly, cut-off points may need to be validated in larger multicenter studies.

CONCLUSION

The HEART score helps in making accurate decisions at the emergency room without the use of radiation or invasive procedures. Low HEART scores go with low likelihood of an ACS and high HEART scores predict high numbers of MACE. In these 2 patient groups, together 53% of patients, proper decisions may be taken based on the HEART score. In case of intermediate values, the HEART score is less helpful and additional diagnostics may be required. The HEART score is an easy, quick, and reliable predictor of outcome in chest pain patients, and can therefore be used for triage.

ACKNOWLEDGMENTS

The authors thank the efforts of cardiologists and residents who kept the medical records. Dr. Fabrice MAC Martens is gratefully acknowledged for his expert support with the ECG classification, and Niels W. Makel for his support with the manuscript preparation.

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Chapter 5

A simple score for the assessment of chest pain patients at the emergency department: a prospective validation study of the HEART score

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Eur Heart Journal (submitted)

Abstract

Aims: The focus of the diagnostic process in chest pain patients at the emergency department is to identify both patients who can be safely discharged and those who should be treated aggressively for an acute coronary syndrome (ACS). The HEART score, with the elements: History, ECG, Age, Risk factors and Troponin was designed to facilitate this process. This study is a prospective validation of the HEART score.
Methods: A total of 2440 unselected patients presented with chest pain at the cardiac emergency department of ten participating hospitals in The Netherlands.The HEART score was assessed as soon as the first lab results and ECG were obtained. Primary endpoint was the occurrence of major adverse cardiac events (MACE) within 6 weeks.
Secondary endpoints were (i) the occurrence of AMI and death, (ii) ACS and (iii) the performance of a coronary angiogram. The performance of the HEART score was compared with the TIMI and GRACE scores.
Results: Low HEART scores (values 0-3) were calculated in 36.4% of the patients. The 6-week MACE endpoint occurred in 1.7% of these patients. In patients with HEART scores 4-6, 46.1% of the study population, MACE was diagnosed in 16.6% of the cases. In patients with high HEART scores (values 7-10), 17.5% of the population, MACE occurred in 50.1% of the cases. Average HEART scores of patients with/without MACE were 6.54 +/- 1.7 and 3.96 +/- 2.0 ($p<0.0001$). With a c-statistic of 0.83 the HEART score is superior as compared to TIMI (0.75) and GRACE (0.70) ($p<0.0001$).
Conclusion: The HEART score for chest pain patients at the emergency department provides the clinician with a quick and reliable predictor of outcome shortly after arrival of the patient, without computer-required calculating. Low HEART scores (0-3), occurring in one third of the patients, exclude short-term MACE with >98% certainty. In these patients one might consider reserved policies. In patients with high HEART scores (7-10) the high risk of MACE may indicate more aggressive policies.
Trial registration: http://www.clinicaltrials.gov NCT01398631

INTRODUCTION

Chest pain is the most common reason for admitting patients to the cardiac emergency department[1,2]. The first challenge in these patients is to identify those with acute coronary syndrome (ACS). This diagnostic process should be quick and efficient, since the prognosis improves dramatically when ACS patients receive targeted treatment as early as possible[3]. In today's practice, approximately 80% of chest pain patients have no clear ACS at presentation[4]. Clinicians tend to postpone the decision making process and to admit these patients for clinical observation, meanwhile treating the patients as an ACS. Consequently, over diagnosis and unnecessary treatment are common, resulting in redundant patient burden and high cost. In order to improve risk stratification of chest patients at the emergency department and to place relative arguments for ACS into perspective, we designed the HEART score (table 1).

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

The HEART score is composed of 5 components: History, Electrocardiogram (ECG), Age, Risk factors and Troponin. For each component 0, 1 or 2 points is given (see methods for further details). HEART was not developed from a database as modern scores often are. The HEART score was based on clinical experience and medical literature and designed to be as easy to use as the Apgar score for newborns[5]. HEART is an acronym of its components: History, ECG, Age, Risk factors and Troponin. Each of these may be scored with 0, 1 or 2 points. We retrospectively evaluated the HEART score in two smaller studies and obtained promising results[6,7]. This resulted in the prospective study in 2440 patients at 10 sites described in this paper. We compared the performance of the HEART score with other scoring systems, such as TIMI[8] and GRACE[9,10,11], although both have been designed for risk stratification of patients with proven ACS and not for the chest pain population at the emergency department.

METHODS

Participants

This study was performed at ten hospitals in the Netherlands. Two sites were academic hospitals exceeding 900 beds each, five sites were large community based hospitals with >500 beds and three sites were smaller community based hospitals with 250-500 beds. Participating hospitals and numbers of included patients are listed in the appendix.
Any patient admitted to the (cardiac) emergency department due to chest pain irrespective of age, pre-hospital suspicions and previous medical treatment was eligible. Patients presenting with only dyspnea or palpitations were not included.
Only patients presenting to the emergency department were eligible for the study. Typically, patients with chest pain and significant ST segment elevations on the ECG during transportation in the ambulance were immediately taken to the nearest available coronary intervention room in the area and, consequently, not presented at the emergency department. Therefore, patients with ST-elevation acute myocardial infarction (STEMI) were only exceptionally included in this study.

The ethics committees of all participating hospitals approved the study. As this was an observational non-intervention study, informed consent procedures were waived. However, patients were informed of the registration of data and the follow up policy.

Data acquisition and management

Emergency department residents of participating hospitals were instructed carefully about the admission CRF and interpretation of the elements of patient history. The resident entered the initial patient data in writing on the admission Case Report Form (CRF), upon arrival of the patient. The CRF consisted of separate entries for classical elements of patient history, cardiovascular risk factors, medication, physical examination and past medical history.

Laboratory values, including troponin I or T levels, were collected throughout the study period, starting with the moment of admission and typically repeated with six hours intervals. A copy of the admission ECG was added to the study files. The ECG was blindly reviewed and classified afterwards by independent, experienced cardiologists. In case of disagreement, a third cardiologist was consulted. A secured web based database was built for this study. An algorithm was devised to calculate the TIMI[8], GRACE[9,10,11] and HEART[6,7] scores automatically from the admission data, without interpretations by the investigators.

HEART score criteria

The HEART score was calculated on admission data only. Data acquired more than one hour after presentation were ignored for score calculations.

History. Patient history was classified based on clinical judgement by the resident in charge, upon arrival of the patient. In absence of specific elements in the patient history for coronary ischemia the history was classified as non-specific and granted zero points. In case the patient history contained both non-specific and suspicious elements, the history was classified moderately suspicious and assigned one point. In case the history contained mainly suspicious elements, such as middle or left sided, heavy chest pain, initiated by exercise, emotions or cold,

radiation and/or relief of symptoms by sublingual nitrates, the history was classified highly suspicious and granted two points. Symptoms recognized by the patient from a previous ACS were also classified as typical.

ECG. The first ECG taken at the emergency department was reviewed and scored. In case of a normal ECG according to Minnesota criteria[12], zero points were given. In case of repolarization abnormalities without ST-segment depression, one point was given. Also in case of the presence of a bundle branch block or pacemaker rhythm, typical abnormalities indicative of left ventricular hypertrophy, repolarization abnormalities probably caused by digoxin use or in case of unchanged known repolarization disturbances, one point was given. In case of ≥ 1mm ST-segment depression in two contiguous leads or elevations or negative T waves in absence of a bundle branch block, left ventricular hypertrophy, or the use of digoxin two points were given.

Age. Zero points were given if the patient was younger than 45 years at the time of admission, one point if the patient was 45 to 65 years and two points if the patient was 65 years or older.

Risk factors. The number of risk factors for coronary artery disease present in the individual was counted. The following risk factors were taken into account: treatment for diabetes mellitus, current or recent (< 90 days) smoker, hypertension, hypercholesterolemia, family history of coronary artery disease, obesity (BMI > 30) or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke or peripheral arterial disease, irrespective of the risk factors for coronary artery disease). If the patient had no risk factors at all, zero points were given. If the patient had one or two risk factors: one point. If the patient had three or more risk factors: two points. Two points were also given if the patient had a history of significant atherosclerosis.

Troponin T or I levels were measured according to local lab standards and reference values (see appendix). Only the troponin value of the first blood sample was used for the HEART score calculation. High sensitive Troponin were not used at any participating hospital at the time of the study conduct. If the Troponin T or I level on admission was below the threshold for

positivity zero points were given. If the level was between once and three times the threshold for positivity: one point. If the level was higher than three times the threshold for positivity: two points.

Follow-up

Follow up data were retrieved from digital and written patient records, including discharge letters, revascularization reports and any other relevant documentation.
In a few cases where follow-up data were not available from hospital records, the patient or their general practitioner was called to obtain information on their condition, hospital admissions, myocardial infarction and revascularization.

Outcomes

The diagnosis of acute myocardial infarction (AMI) was made according the applicable guidelines when the protocol was written, the joint ESC-ACCF-AHA-WHF task force for the redefinition of myocardial infarction[13], and consisted of a rise and or fall of troponin values with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia. Within the diagnosis of AMI, distinction was made between either:
ST-elevation myocardial infarction (STEMI), defined as a syndrome consisting of a rise and fall of troponin values as described above, typical patient history and transient ST segment elevations on the consecutive 12 lead ECGs, or:
non ST-elevation myocardial infarction (NSTEMI), defined as a syndrome consisting of a rise and fall of troponin values as described above, typical patient history and persistent or transient ST-segment depression or T-wave inversion, flat T-waves, pseudo-normalization of T-waves, or no changes at presentation.
In case of rises of troponin levels without evidence of myocardial ischemia or in case of non-availability of data the case was discussed in the adjudication committee where a final diagnosis was made according to the guidelines [3,13,14].

Percutaneous coronary intervention (PCI) was defined as any therapeutic catheter intervention in the coronary arteries. Coronary artery bypass graft (CABG) surgery was defined as any cardiac surgery in which coronary arteries were operated on.

The primary endpoint in this study was the occurrence of a major adverse cardiac event (MACE), within six weeks of initial presentation. MACE consists of: AMI, PCI, CABG, coronary angiography revealing procedurally correctable stenosis managed conservatively, and death due to any cause.
Coronary angiography revealing procedurally correctable stenosis managed conservatively was defined as significant coronary stenosis thought to be the cause of the chest pain, but revascularization was withheld for reasons of co-morbidity or risk of complications.

Secondary endpoints

Secondary endpoints were:
(i) the six-week occurrence of AMI and death,
(ii) the diagnosis of ACS within three months after presentation. The spectrum of ACS was described according to the definitions in the guideline for non-ST-segment elevation acute coronary syndrome[3,14] and consisted of:
definite ACS, defined as: STEMI or NSTEMI (as defined above), or suspected ACS, defined as: likely to be an ACS based on typical patient history consistent with unstable angina and/or ST segment depression or T wave inversion or significant stenosis at coronary angiography, but without a rise of troponin levels,
(iii) the performance of coronary angiography within three months after presentation.

Statistical analysis

Statistical analysis was performed with R (Version 2.9; The R foundation for Statistical Computing, Vienna, Austria)[15]. Descriptive statistics are given as average +/- SD, percentage or Kaplan-Meier cumulative event-free curve. Differences between groups were assessed by means of the Student's t-test when normally distributed. For scalar data we used the Fisher's exact test, or for ordinal data the Cochran-Armitage Trend Test.
The probability of reaching an endpoint was calculated as the percentage of cases with an endpoint within a given category. The area under the receiver operator characteristic curve (c-statistic) was computed in order to give a measure of diagnostic discriminative strength, combining sensitivity and specificity, especially for non-binomial variables. The DeLong's test was used

for testing two correlated ROC curves**.** Statistical significance was defined as p<0.05 two-sided.

RESULTS

Study population

The patient inclusion period lasted from October 2008 to November 2009. A total of 2440 patients were included. Seven patients (0.3%) were non-evaluable due to invalid data on admission. In another 45 cases (1.8%) the 6-week follow up was incomplete. These patients were all discharged after short observation. In this subgroup the average age was 43.8 +/- 15.8 years and the HEART score 2.3 +/- 1.9 (mean +/- SD). The study population consisted of the remainder of 2388 patients with a follow up duration of 222+/- 127 days (mean +/- SD). The total follow up duration of the entire study group was 1449 patient years. Patient characteristics of the study group are presented in table 2.

Table 2. Patient characteristics

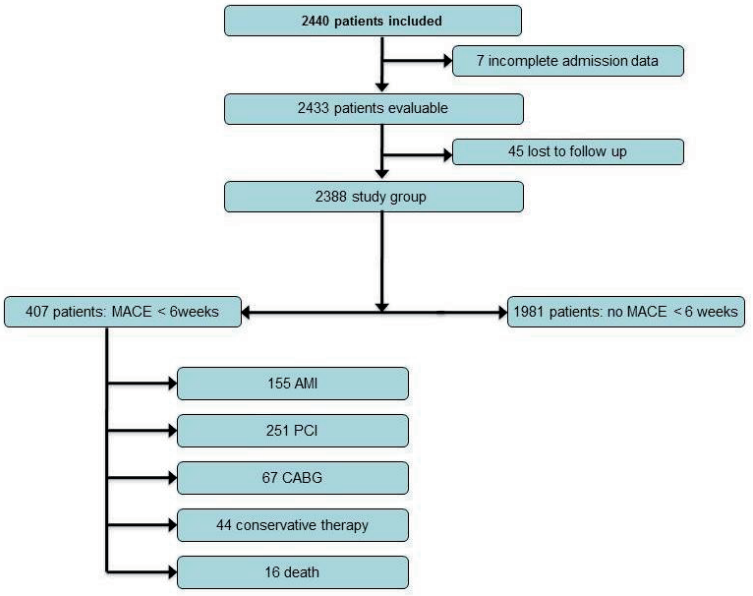
	N	SD	%
Study group	2388		100
Mean age	60.6	15.4	
Male gender	1372		57.5
Diabetes Mellitus	444		18.6
Smoker	779		32.7
Hypercholesterolemia	856		35.8
Hypertension	1034		43.3
Family History	866		36.3
Obesity	582		24.4
Mean systolic blood pressure	141.4	24.3	
Mean diastolic blood pressure	78.1	21.9	
History of AMI	379		15.9
History of CABG	243		10.2
History of PCI	510		21.4
History of Stroke	112		4.7
History of peripheral arterial disease	110		4.6

AMI = acute myocardial infarction. CABG = coronary artery bypass graft. PCI = percutaneous coronary intervention.

Patient flow

The patient flow in the HEART study is given in figure 1.

Figure 1. Patient flow in the HEART score validation study.



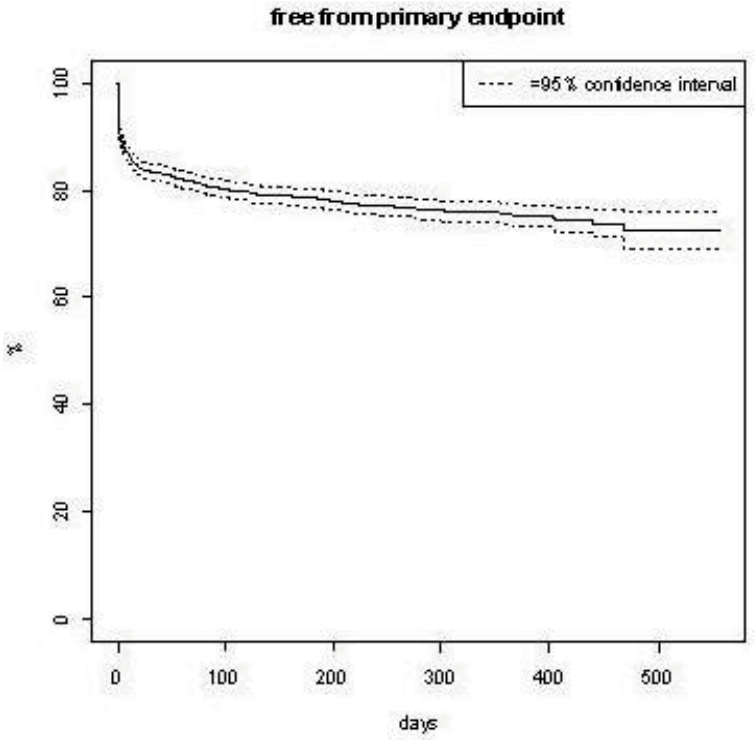
AMI = acute myocardial infarction. CABG = coronary artery bypass graft. PCI = percutaneous coronary intervention. MACE = major adverse coronary events.

Primary end points

Of a total of 2388 patients 407 (17.0%) were diagnosed with MACE within 6 weeks: AMI was diagnosed in 155 patients (6.4%), 251 patients (10.5%) underwent PCI, 67 patients (2.8%) had a CABG and 44 patients (1.8%) had coronary angiography revealing procedurally correctable stenosis managed conservatively. Sixteen patients (0.7%) died within 6 weeks after presentation, of which 13 patients due to cardiovascular causes. Altogether, 533 major events occurred in 407 patients: an average of 1.30 events (MACE) per patient.
142/155 AMIs (91.6%) were diagnosed at presentation: 110 NSTEMI, 18 STEMI and 14 recent AMI (onset 12-48 hours before presentation). Mean duration of time to AMI was 0.3 days (range 0-17). 165/407 (40.8%) of MACE were reached at presentation. Mean duration of time to MACE was 5.6 days (range 0-41). Mean

time to PCI 6.9 days (0-41), mean time to CABG 12.1 (1-39) days and mean time to death 13.6 days (1-33). The time elapsed between arrival of the patient and the occurrence of MACE is given in figure 2.

Figure 2. Kaplan-Meier curves for the occurrence of major adverse cardiac events.



The HEART score

The numerical distribution of the HEART score's five elements in the groups with or without endpoints is shown in table 3.The five elements of the HEART score differed significantly between the groups with and without MACE. The average HEART score was 3.96 +/- 2.0 in the non-MACE group and 6.54 +/- 1.7 in the MACE group.

Table 3. Number of patients in each element of the HEART score

	No MACE < 6w						MACE < 6w						p value for trend
	n = 1981						n = 407						
Points	**0**	**%**	**1**	**%**	**2**	**%**	**0**	**%**	**1**	**%**	**2**	**%**	
History	902	45.5	616	31.1	462	23.3	35	8.6	110	27.0	262	64.4	p=0.000
ECG	1323	66.8	380	19.2	278	14.0	147	36.1	86	21.1	174	42.8	p=0.000
Age	376	19.0	862	43.5	743	37.5	15	3.7	171	42.0	221	54.3	p=0.000
Risk Factors	221	11.2	729	36.8	1031	52.0	20	4.9	116	28.5	271	66.6	p=0.000
Troponin	1825	92.1	89	4.5	67	3.4	218	53.6	55	13.5	134	32.9	p=0.000

MACE = Major Adverse Cardiac Events. ECG = electrocardiogram.

The c-statistic of the HEART score in the entire study group was 0.83. The HEART score retained its discriminative ability in three relevant subgroups: in diabetics the event rate was 81/440 with a c-statistic of 0.78 (non-diabetic 0.84), in females (event rate 116/1016) the c-statistic was 0.83 (males 0.82) and in elderly over the age of 75 (event rate 101/490) the c-statistic was 0.73 (age≤75 0.86).

Three scores

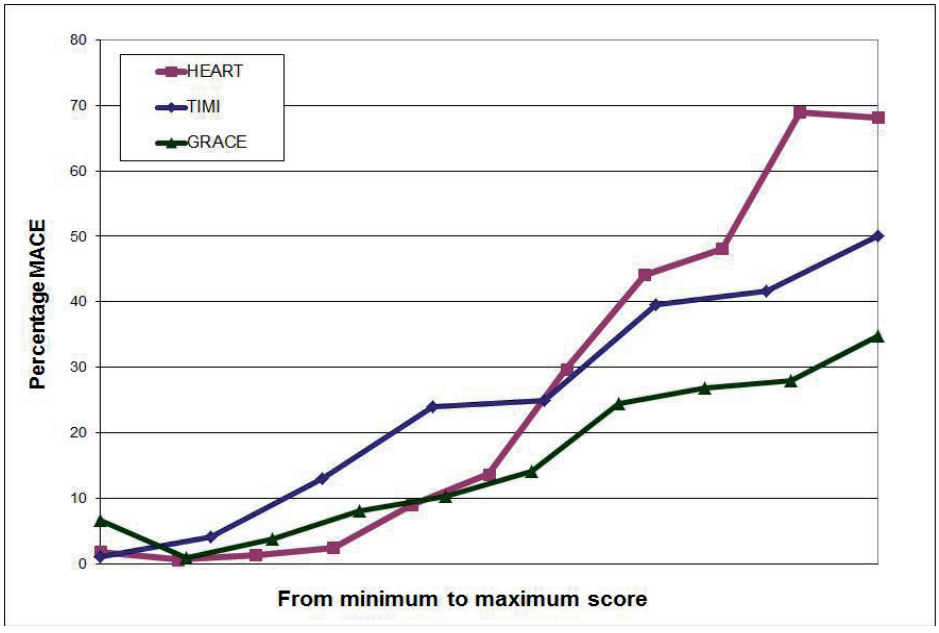
Average values of the three scores in groups with and without MACE are given in table 4. All scores differed considerably between the group free from MACE and the group with MACE. Figure 3 illustrates the relation between the scores (on the x-axis) and the risk of MACE within 6 weeks after initial presentation (on the y-axis).
Comparison of the c-statistics as represented in table 4 shows a value of 0.83 for the HEART score, 0.75 for TIMI and 0.70 for GRACE. The HEART score performed significantly better ($p<0.001$) as compared with TIMI and GRACE.

Table 4. Average values of the three scores in patients with chest pain presenting at the emergency department in groups with and without MACE

	Total study population	No MACE<6w n = 1981	MACE<6w n = 407	C-statistic	p value
HEART	4.4 (2.2)	3.96 (2.0)	6.54 (1.7)	0.83	<0.0001
TIMI	2.5 (1.7)	2.21 (1.6)	3.68 (1.4)	0.75	<0.0001
GRACE	99.9 (36.1)	95.5 (35.0)	121.2 (34.0)	0.70	<0.0001

Averages are given as mean (SD).

Figure 3. Probability of reaching a MACE related to the three risk scores.



Only for the purpose of comparing graphs we divided the TIMI and GRACE scores in deciles in order to achieve the same distribution as the HEART score on the x-axis. All other computations were made with the original values.

Predictive values of low scores

The low risk boundaries for all scores were set at a risk of MACE < 5%. In the group with TIMI scores of 0-1, which accounted for 34.0% of the study population, 23/811 (2.8%) had a MACE. The 14.0% of the patients who had GRACE scores 0-60 had MACE in 10/335 (2.9%) of the cases. The group with a low HEART score (values 0-3) represents 36.4% of the study population. Six-week MACE occurred in 15/870 (1.7%) of these patients. This included nine AMIs, nine PCI, three CABG and one death. This 20 year old male committed suicide, seven days after the index chest pain event.

Predictive values of intermediate scores

The intermediate risk boundaries for all scores were set at a risk of MACE between 5 and 40%. In the group with TIMI scores of 2-5, which accounted for 62.7% of the study population, 350/1497 (23.4%) had a MACE. The 85.7% of the patients who had GRACE scores >60 had MACE in 389/2012 (19.3%) of the cases. The group with an intermediate HEART score (values 4-6) represents 46.1% of the study population. Six-week MACE occurred in 183/1101 (16.6%) of these patients.

Predictive values of high scores

Only the TIMI and HEART scores reached a high risk level, defined as a risk of MACE > 40%. MACE occurred in 34/80 patients (42.5%) where TIMI scores were 6-7. The group with a high HEART score (7-10) represents 17.5% of the study population; six-week MACE occurred in 209/417 (50.1%) of those patients.

Secondary endpoints

A total of 164/2388 (6.9%) patients had an AMI (n=155) or died (n=16) within six weeks. The c-statistics for the occurrence of AMI or death of HEART, TIMI and GRACE are 0.82, 0.70 and 0.71 respectively ($p<0.0001$).

An ACS within three months after presentation was diagnosed in 536 patients (22.4%); 501 of these 536 ACS (93.4%) were already diagnosed during primary admission.

The c-statistics for the occurrence of ACS shows a value of 0.86 for the HEART score, 0.78 for TIMI and 0.72 for GRACE ($p<0.0001$).

Coronary angiography within three months was performed in 578 patients (24.2%). In 93 (16.2%) of these cases this diagnostic procedure was performed during primary admission. The results were: 58 (10.0%) normal coronaries, 104 (17.9%) non-significant stenosis, 44 (7.6%) significant stenosis with conservative treatment, 361 (62.4%) significant stenosis requiring revascularization and 11 (1.9%) were unclassified.
The HEART score was 3.9 +/- 2.0 in the group with no catheterization in the first three months and 6.0 +/- 1.8 in the group with a catheterization in the first three months ($p < 0.001$).

DISCUSSION

The use of the HEART score for chest pain patients at the emergency department provides the clinician with a reliable predictor of outcome, very soon after the arrival of the patient, based on already available clinical data and without computer-required calculating.

The favorable results of this large prospective validation study confirm our previous retrospective evaluation studies[6,7]. A c-statistic of 0.83 for the HEART score indicates a good to excellent ability to discriminate all chest pain patients at the emergency department for their risk of MACE. The HEART score facilitates communication, as it provides all crucial information to correctly place patients into low, intermediate and high risk groups. In addition, it closely follows clinical thinking. Less complex guidelines for clinical practice can be formulated when advised policies are based on a HEART score stratification.

Several risk scores for ACS have been published[16]. The most reputable of these are the TIMI[8] and GRACE[9,10,11] scores. Both were developed for risk stratification of patients admitted to the coronary care unit with an ACS, and may take observations at arbitrarily chosen points in time into account. Although not designed for this purpose, these scores are applied at the emergency department for the whole range of chest pain patients, both in practice and in science[1,4,17,18]. Different from this, the HEART score was specifically designed for the much broader chest pain population at the emergency department. HEART is based on admission data only, typically complete within one hour. This score is now validated in a prospective manner.

Both TIMI and GRACE are recommended in European and American guidelines[3,14] for the risk stratification of patients suspected of ACS upon arrival at the emergency department but many hospitals do not follow these guidelines[19]. Neither the TIMI nor the GRACE score appreciates the specificity of patient history (anamnesis), even though clinicians rely heavily on this and guidelines advise to use patient history for making a diagnosis[3,14,20, 21]. Some other scores, such as PURSUIT[22], FRISC[23] and SRI[24] are less specific and to some extent outdated, as troponin levels are not part of it; therefore, these are not reported in this paper.

The GRACE score is a well-validated prediction model of death in ACS patients. A practical disadvantage of the GRACE score is that it can only be calculated by means of a computer. Although it was not designed for making or excluding the ACS diagnosis in an unselected chest pain population, we applied the GRACE score in the chest pain setting at the emergency department. We found that the points given for 'age' accounted for 50.0 +/- 18.3 % of the total number of GRACE points. Not surprisingly, higher age is related to higher mortality rates. Whether the predominantly age based GRACE score helps the clinician to choose the right treatment option is questionable. Should medicine become more aggressively with increasing ages? We think most clinicians disagree. All things considered, the GRACE score performs poorer than TIMI and HEART.

The TIMI score, which was designed about 15 years ago for identifying high-risk ACS patients who benefit most from aggressive anti-clotting agents, is relatively easy to calculate. However, it is quite rough as it allows only binary choices, thus ignoring the fact that many variables have a 'grey area.' Than and co-investigators applied the TIMI score for the broad chest pain population at the cardiac emergency departments of 14 hospitals in 9 countries in the Asia-Pacific region[4]. In their prospective multi-center study 9.8% of the patients had a TIMI score = 0 assessed after 2 hours and those patients had a 4-week risk of MACE of 0.9%. In our study at 10 sites in the Netherlands 36.4% of the patients had HEART scores 0-3 within 1 hour, indicating a 6-week risk of MACE of 1.7%. Although the comparison is hampered to some extent by differences in end point definitions,

we believe that the approach in the Pacific study may benefit significantly from the replacement of the TIMI score by the HEART score[25].

When comparing the GRACE, TIMI and HEART in terms of predictive values for low- and high-risk, and the c-statistics, we conclude that the HEART score is the best score in the setting of chest pain at the emergency department.

Other than in randomized trials, loss to follow up is an inevitable reality in an observational study at the emergency department: occasional visitors occur and they are sometimes hard to track afterwards. Our clinical review of the characteristics showed that the 45 patients lost to follow up (1.8% of the entire study population) were relatively young visitors with low likelihood of disease.

A six-week study period was chosen, as events occurring within this time frame are believed to be the result of an index ACS. However, the causal relation between the index chest pain syndrome and consecutive events is not as clear as it seems. Both an ACS without MACE and a MACE without ACS may occur in chest pain patients. No study can tell us the true incidence of both situations. Although MACE is a 'hard' endpoint, it is no more than an objective indicator of an ACS for academic purposes and does not replace a clinical diagnosis that is subjective by nature.

The HEART score gives immediate direction to the treatment policy. Over one third of our patients had HEART scores 0-3. This observation may be a firm basis to omit redundant diagnostic and treatment steps and move into the direction of quick discharge. This issue was also addressed recently by Mahler and coworkers[26]. In a retrospective study in low-risk chest pain patients from North Carolina (USA) they found a 0.6% risk of MACE in 904 patients with HEART scores ≤ 3. The authors state "… the HEART score could substantially reduce cardiac testing in a population with low pretest probability of ACS". The group of high-risk patients (HEART scores 7-10) in our study concerns 17.5% of the entire study population. With a risk of MACE of 50.1% in these patients quick coronary intervention should be warranted according to studies by others[16,27,28,29]. Obviously, the early direction given by the HEART score should not prevent the treating physicians from further clinical thinking. In

many patients the observation should continue for some more hours, with repeated troponins and ECGs, in order to confirm initial findings.

CONCLUSION

In conclusion, the HEART score for chest pain patients at the emergency department provides the clinician with a quick and reliable predictor of outcome shortly after arrival of the patient, without computer-required calculating. Low HEART scores (0-3), occurring in one third of the patients, exclude short-term MACE with >98% certainty. In these patients one might consider reserved policies. In patients with high HEART scores (7-10) the high risk of MACE may indicate more aggressive policies.

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APPENDIX

Participating hospitals, principal investigators and numbers of patients in the study		
Hospital	**Investigators**	**Patients**
Universitair Medisch Centrum (Groningen)	René Tio, Iwan van der Horst, Marco Willemsen	464
St Antonius Ziekenhuis (Nieuwegein)	Gijs Mast, ThijsPlokker	455
Meander Medisch Centrum Amersfoort	Arend Mosterd, Jeff Senden	381
Gelre Ziekenhuis (Apeldoorn)	Richard Braam, Bjorn Groenemeijer, Luc Cozijnsen	257
Medisch Centrum Haaglanden (Den Haag)	Alexander Wardeh, WouterTietge	218
Reinier de Graaf Groep (Delft)	Stefan Monnink, Eelko Ronner	170
Medisch Centrum Haaglanden (Leidschendam)	Rolf Veldkamp	183
Antonius Ziekenhuis locatie Oudenrijn (Utrecht)	Rob van Tooren	118
Universitair Medisch Centrum (Utrecht)	Pieter Doevendans, Maarten-Jan Cramer	106
ZuweHofpoort Ziekenhuis (Woerden)	Jacob Six, Bert Brinkman, Jan Slob and Bettina Massaar-Hagen	81
Total		2433

Reference values troponin.

Hospital	Troponin T or I	Reference value
1	T	0.015
2	T	0.015
3	I	0.040
4	I	0.050
5	I	0.100
6	I	0.030
7	I	0.030
8	T	0.010
9	T	0.010
10	T	0.010

Chapter 6

The HEART score for chest pain patients at the emergency department validated in a multi centre Asia-Pacific population

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CMJA (submitted)

ABSTRACT:

Background: The HEART score for the early risk stratification of patients presenting to Emergency Departments (EDs) with chest pain contains five elements: History, ECG, Age, Risk factors and Troponin. It has been locally validated in The Netherlands. The purpose of this investigation was to perform an external validation of the HEART score in patients within the Asia-Pacific region.
Methods: Data was used from 2906 patients presenting with chest pain to the EDs of 14 hospitals. The HEART scores were calculated without subjective interpretations. The predictive values for the occurrence of 30-day major adverse coronary events (MACE) were assessed. A comparison was made with the Thrombolysis in Myocardial Infarction (TIMI) score.
Findings: The low-risk group, defined as HEART score ≤ 3, consisted of 820 patients, who represented 28.2% of the study population. Fourteen (1.7%) patients were incorrectly defined as low risk (false negatives). The high-risk population, defined as a HEART score of 7-10 points, consisted of 464 patients (16%) who had a risk of MACE of 43.1%. The values of the C-statistic were 0.83 (0.81-0.85) for the HEART score and 0.75 (0.72-0.77) for the TIMI score ($p<0.01$).
Interpretation: Utilization of the HEART score provided excellent determination of risk for 30-day MACE, comparing well with the TIMI score. This study externally validates previous findings that the HEART score is a powerful clinical tool in this setting. Within one hour from presentation, it identifies both (i) a large proportion of low-risk patients, in whom early discharge without additional testing goes with a risk of MACE of only 1.7%, and (ii) high-risk patients who are potential candidates for early invasive strategies.

INTRODUCTION

The recently described HEART score is designed specifically for the early risk stratification of patients presenting with chest discomfort of suspected cardiac origin to the emergency department (ED)[1,2,3]. It categorizes patients using five elements comprising the acronym of the HEART score: History, ECG, Age, Risk factors and Troponin. Each of these may be scored with 0, 1 or 2 points with a maximum score of 10 points. Existing validation of the HEART score includes a retrospective study in 880 patients [2] (including a previously published pilot in 122 patients [1]) and a prospective study in 2440 patients conducted in a single country (the Netherlands)[3]. In both studies about one third of the patients with chest pain had HEART scores 0-3, with a 6-week incidence of major adverse coronary events (MACE) of 1-2%.

Recently a prospective observational validation study of a predefined 2-h accelerated protocol in patients presenting with chest pain to the ED of 14 hospitals in the Asia-Pacific region (the ASPECT study) was published in Lancet[4]. The ASPECT study evaluated the value of the Thrombolysis In Myocardial Infarction score for unstable angina (TIMI score)[5] in combination with ECG and a point-of-care biomarker panel (of troponin, creatine kinase-MB, and myoglobin) to predict the incidence of MACE at 30 days from hospital attendance. The main conclusion was that a TIMI score = 0 in combination with biomarkers and ECG identified a group of 9.8% of the patients who have a risk of only 0.9% of the MACE endpoint. It has been suggested that the TIMI score would better be replaced by the HEART score[6].

External validation studies of risk scores outside the original derivation and validation centers are uncommon. However, they are important in order to assess the applicability of the risk scores in other locations and populations. The investigators of the ASPECT and HEART groups have now collaborated to analyze an extended database from the Asia-Pacific region. The purpose of this investigation was to carry out such an external validation of the HEART score in a different international setting.

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

METHODS

The ASPECT database

Patients presenting with chest discomfort of at least 5 min duration suggestive of acute coronary syndromes (ACS) for whom the attending physician planned to investigate for these syndromes with serial biomarker tests within 14 hospitals in 9 countries: Australia, China (including Hong Kong), India, Indonesia, New Zealand, Singapore, South Korea, Taiwan, and Thailand. Patients were enrolled as part of the ASPECT study with additional patients from the Australia-New Zealand Acute Chest Pain (ANZACP) registry, which is an ongoing registry of the investigation, management and outcomes of patients presenting to two Australasian hospitals with chest pain of possible cardiac

origin. The cohort reported in this study includes, but is not limited to, the study population that has been published previously[4].

In accordance with American Heart Association case definitions[7], possible cardiac symptoms included acute chest, epigastric, neck, jaw, or arm pain; or discomfort or pressure without an apparent non-cardiac source. Patients were excluded if there was a clear cause other than an acute coronary syndrome for the symptoms (e.g., clinical findings of pneumonia), they were unable or unwilling to provide informed consent, staff considered recruitment to be inappropriate (e.g. terminal illness), they were transferred from another hospital, they were pregnant, they were recruited on previous presentation, or they were unable to be contacted after discharge. Patients were also excluded from this dataset if their first ECG had ST-segment elevation or if they did not have complete data to enable calculation of the HEART score.

Recruitment included consecutive eligible cases at each site. Overall enrolment for this data set analysis occurred between November 2007, and December 2010, but individual sites started and finished at different times according to local logistics. Patients were managed according to local protocols.

HEART score criteria

The HEART score was calculated using data collected on admission only. The elements were defined as follows.

***History*.** Patient history was classified according to a mutually agreed distinction between elements of typical or atypical angina. Patients were categorized with typical pain if they presented with central or left sided chest pain with radiation to the arms or throat or sweating or clamminess. Patients were categorized with atypical pain if they presented without chest pain or with right-sided chest pain or pain that radiated to the back or worsened on inspiration or palpation. Within the HEART score, *0 points* were given for patients with atypical pain only, *1 point* when the patient had elements of both typical and atypical pain and *2 points* when the patient had typical pain only.

ECG. The original CRF contained six yes/no questions about the admission ECG. With regards to ECG findings, *0 points* were given if the ECG was normal or had non-specific ST-T wave changes, *1 point* was given if it was abnormal but not diagnostic

of ischemia (e.g. bundle branch block and pacemaker rhythm) or if there was evidence of pre-existing changes of ischemia or previous infarction, *2 points* were given. If there were finding of infarction or ischemia not known to be old or consistent with an acute myocardial infarction.
Age. *0 points* were given if the patient was younger than 45 years at the time of admission, *1 point* if the patient was 45 to 65 years and *2 points* if the patient was 65 years or older.
Risk factors. The number of risk factors for coronary artery disease present in the individual was counted. The following risk factors were taken into account: diabetes mellitus, current or recent (< 90 days) smoker, hypertension, hypercholesterolemia, family history of coronary artery disease. If the patient had no risk factors, *0 points* were allocated. If the patient had one or two risk factors: *1 point*. If the patient had three or more risk factors*: 2 points*. *Two points* were also given if the patient had a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke or peripheral arterial disease).
Troponin T or I. Levels were measured according to local laboratory standards; details are given in the previous publication[4]. Only the troponin value of the first blood sample taken on arrival was used for the HEART score calculation. An elevated troponin was defined as a value greater than the 99th percentile for the assay, as reported by the manufacturer (www.ifcc.org). If the troponin T or I level on admission was equal to, or less than the 99th percentile *0 points* were allocated. If the level was between once and three times the 99th percentile: *1 point*. If the level was equal to or higher than three times the 99th percentile: *2 points*.

Endpoint classification

The primary endpoint was MACE within 30 days of initial presentation (including initial hospital attendance). The criteria for MACE included any of the following: acute myocardial infarction (AMI), emergency percutaneous coronary intervention (PCI) coronary artery bypass graft (CABG), or death (not clearly non-cardiac). The secondary endpoint included AMI, CABG, cardiac death or any PCI (including emergency, urgent and elective).

The diagnosis of AMI was based on global taskforce recommendations requiring evidence of myocardial necrosis together with evidence of myocardial ischemia (ischemic symptoms, ECG changes, or imaging evidence)[8]. Necrosis was diagnosed on the basis of a rising or falling pattern of the laboratory cardiac troponin concentrations, with at least one value above the 99th percentile, at a level of assay imprecision near to 10%. If the troponin concentration was greater than the reference range, but no rise or fall was recorded, other causes of a raised troponin concentration were carefully considered by the adjudicating cardiologist. If no clear alternative cause of the troponin rise was apparent, and if the clinical presentation was suggestive of an ACS, an adjudicated diagnosis of acute myocardial infarction was made.

PCI was defined as any therapeutic catheter intervention in the coronary arteries. CABG surgery was defined as any cardiac surgery that involved an operation of the coronary arteries.

Statistics

Data were collected with the web-based open-clinical data capture system. Baseline characteristics of the study population were analyzed with conventional group descriptive statistics. Descriptive statistics are given as average +/- SD. The c-statistic was calculated to determine the discriminative power of the HEART score and Chi square analyses were used to generate two-by-two tables for the calculation of sensitivity, specificity, and positive and negative predictive values. The TIMI score was also calculated using the initial troponin result only in order to match biomarker use in the HEART score. The c-statistic and diagnostic accuracy of TIMI was calculated to enable comparison to the HEART score. Analyses were done with SPSS (version 19.0).

The ASPECT study and the ANZACP registry are registered with the Australia-New Zealand Clinical Trials Registry, number ACTRN12609000283279 and ACTRN12611001076965 respectively.

RESULTS

There was a participant population of 3193 consecutive patients from which 287 patients were removed due to missing endpoints data at 30 days giving a final sample of 2906 patients available for analysis.

Patients were mostly older males and of Chinese (22.7%) or Caucasian (58.8%) origin. There were 374 (12.9%) patients with a major adverse cardiac event within 30 days. Diagnoses included STEMI (19 patients) and NSTEMI (353 patients). Nineteen patients (0.7%) underwent emergency revascularization with PCI or CABG, and 9 patients (0.3%) died within 30 days of admission. 493 (17%) patients met the definition for the secondary endpoint within 30 days. This figure incorporates 195 (6.7%) patients who had an urgent revascularization and 64 (2.2%) who had an elective revascularization within 30 days.

Table 2. Baseline characteristics of analysed participants with and without major adverse cardiac event (MACE).

	No MACE n=2532	**MACE n=374**	**p**
Age, Mean (SD)	59.7 (14.6)	68.4 (13.25)	<0.01
Male, n (%)	1491 (58.9)	263 (70.3)	<0.01
Diabetes, n (%)	457 (18.0)	100 (26.7)	<0.01
Smoker (Current or Recent), n (%)	534 (21.1)	75 (20.1)	0.65
Hypercholesterolemia, n (%)	1073 (42.4)	195 (52.1)	<0.01
Hypertension, n (%)	1341 (53.0)	247 (66.0)	<0.01
Family History of Coronary Artery Disease, n (%)	1029 (40.6)	179 (47.9)	<0.01
History of myocardial infarction, n (%)	500 (19.7)	126 (33.7)	<0.01
History of CABG, n (%)	170 (6.7)	51 (13.6)	<0.01
History of PCI, n (%)	445 (17.6)	76 (20.3)	0.20
History of Stroke, n (%)	234 (9.2)	49 (13.1)	0.02
History of peripheral art disease, n (%)	56 (2.2)	21 (5.6)	<0.01

Table 2 provides baseline characteristics of the sample with and without major adverse cardiac event. Patients with MACE were older and more likely to be male. They also had a higher proportion of diabetes, hypercholesterolemia, hypertension, family history of coronary artery disease, history of MI, CABG, stroke and peripheral arterial disease.

The relationship between the five predefined elements of the HEART score and the occurrence of endpoints is given in Table 3. Patients with MACE were more likely to have a specific history, have an abnormal ECG, be older, have risk factors and have an elevated troponin level. The average HEART score was significantly higher in patients with MACE than without MACE. The distribution of HEART scores in patients with and without MACE is provided in Figure 1.

Figure 1. The distribution of heart scores in patients with and without major adverse cardiac event (MACE).

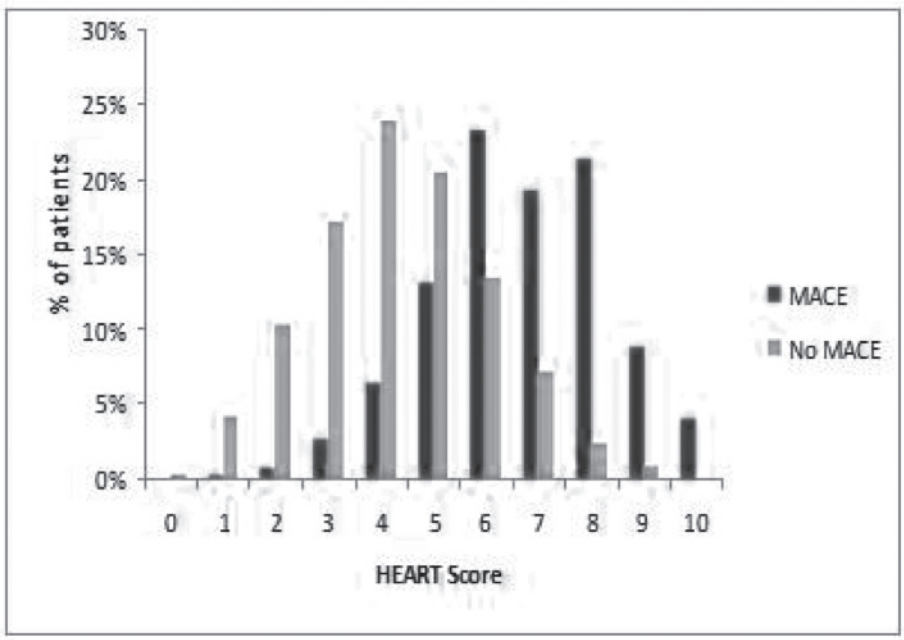
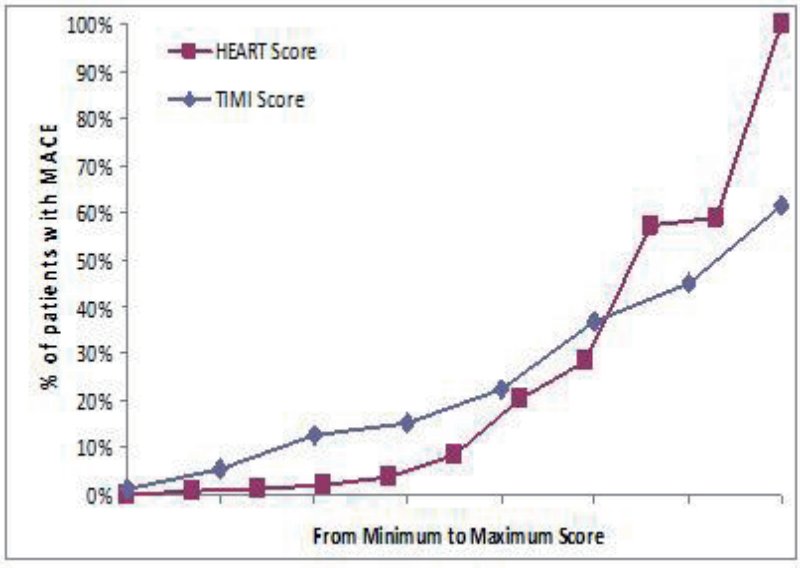


Table 3. The relationship between the five predefined elements of the HEART score and the occurrence of major adverse cardiac event (MACE) and secondary endpoints.

	No MACE n=2532			**MACE n=374**			**p**
Points	**0**	**1**	**2**	**0**	**1**	**2**	
History	324 (12.8)	1304 (51.5)	904 (35.7)	21 (5.6)	152 (40.6)	201 (53.7)	<0.01
ECG	1700 (67.1)	546 (21.6)	286 (11.3)	212 (56.7)	66 (17.6)	96 (25.7)	<0.01
Age	426 (16.8)	1148 (45.3)	958 (37.8)	21 (5.6)	120 (32.1)	233 (62.3)	<0.01
Risk Factors	334 (13.2)	1060 (41.9)	1138 (44.9)	24 (6.4)	129 (34.5)	221 (59.1)	<0.01
Troponin	2313 (91.4)	142 (5.6)	77 (3.0)	67 (17.9)	92 (24.6)	215 (57.5)	<0.01
Heart Score (aver. +/- SD)	**4.32 (+/-1.70)**			**6.66 (+/-1.70)**			**<0.01**
	No Secondary Endpoint n=2413			**Secondary Endpoint n=493**			**p**
Points	**0**	**1**	**2**	**0**	**1**	**2**	
History	313 (13.0)	1249 (51.8)	851 (35.3)	32 (6.5)	207 (42.0)	254 (51.5)	<0.01
ECG	1630 (67.6)	520 (21.5)	263 (10.9)	282 (57.2)	92 (18.7)	119 (24.1)	<0.01
Age	419 (17.4)	1079 (44.7)	915 (37.9)	28 (5.7)	189 (38.3)	276 (56.0)	<0.01
Risk Factors	326 (13.5)	1022 (42.4)	1065 (44.1)	32 (6.5)	167 (33.9)	294 (59.6)	<0.01
Troponin	2202 (91.3)	139 (5.8)	72 (3.0)	178 (36.1)	95 (19.3)	220 (44.6)	<0.01
Heart Score (aver. +/- SD)	**4.29 (+/-1.71)**			**6.24 (+/-1.80)**			**<0.01**
N (%)							

Figure 2. Values for the HEART and TIMI scores, and the risk of MACE



The predictive value of HEART scores for the occurrence of MACE was calculated and a comparison was made with the TIMI score (Figure 2). The risk of subsequent MACE and secondary endpoints in each HEART score category of patients is given in table 4.

Table 4. The risk of reaching a MACE and a secondary endpoint in each HEART category of patients.

HEART score	0	1	2	3	4	5	6	7	8	9	10	Total
MACE (Primary Endpoint)												
n pts	8	106	263	443	627	567	428	253	140	56	15	2906
n MACE pts	0	1	3	10	24	49	87	72	80	33	15	374
% MACE	0	0.9	1.1	2.3	3.8	8.6	20.3	28.5	57.1	58.9	100	12.9
Secondary Endpoint												
n Secondary Endpoint	0	2	7	20	58	82	107	85	82	35	15	493
% Secondary Endpoint	0	1.9	2.7	4.5	9.3	14.5	25.0	33.6	58.6	62.5	100	17.0

There is no internationally agreed definition of low risk for MACE. If “low risk” is defined as a risk < 2%, the cut off level for the HEART score is ≤2 points. Under that definition, 4/377 patients with a heart score ≤2 were false negative (1.1%). Previous research utilizing the HEART score defined “low risk” as HEART score ≤3 points. Using this cut-off, 14/820 patients (1.7%) patients were incorrectly defined as low risk (false negatives).

With the TIMI score set at 0 points, there were 7/521 (1.3%) false negative cases. With the TIMI score set at ≤ 1 point, 47/1249 (3.8%) patients were incorrectly defined as low risk.

The values for sensitivity, specificity and predictive values of negative and positive tests of both the HEART and TIMI scores are given in table 5.

Table 5. Sensitivity, specificity and predictive values for the occurrence of MACE in patients with low HEART or TIMI scores.

	HEART ≤ 2	HEART ≤ 3	TIMI = 0	TIMI ≤ 1
Primary Endpoint				
Sensitivity	98.9 (97.3-99.6)	96.3 (93.8-97.8)	98.1 (96.2-99.1)	87.4 (83.7-90.4)
Specificity	14.7 (13.4-16.2)	31.8 (30.0-33.7)	20.3 (18.8-21.9)	47.5 (45.5-49.4)
Positive Predictive Value	14.6 (13.3-16.1)	17.3 (15.7-18.9)	15.4 (14.0-16.9)	19.7 (17.9-21.7)
Negative Predictive Value	98.9 (97.3-99.6)	98.3 (97.2-99.0)	98.7 (97.3-99.3)	96.2 (95.0-97.2)
Secondary Endpoint				
Sensitivity	98.2 (96.6-99.0)	94.1 (91.7-95.9)	96.3 (94.3-97.7)	84.2 (80.7-87.1)
Specificity	15.3 (13.9-16.7)	32.8 (30.9-34.7)	20.8 (19.3-22.5)	48.5 (46.5-50.5)
Positive Predictive Value	19.1 (17.7-20.7)	22.2 (20.5-24.1)	19.9 (18.4-21.6)	25.0 (23.0-27.2)
Negative Predictive Value	97.6 (95.5-98.7)	96.5 (95.0-97.5)	96.5 (94.6-97.8)	93.8 (92.3-95.0)
Value (95% confidence limits)				

Using MACE as the outcome, the values of the C-statistic were 0.83 (0.81-0.85) for the HEART score and 0.75 (0.72-0.77) for the TIMI score ($p<0.01$). The C-statistic of the HEART score in Caucasians was 0.83 (0.80-0.86) and in Chinese 0.83 (0.77-0.88). For the secondary outcome, values of the C-statistic were 0.78 (0.76-0.80) for HEART and 0.72 (0.70-0.75) for TIMI ($p<0.01$).

There were 820 patients with a HEART score between 0 and 3 and 14 of these had a MACE at 30 days. These patients were diagnosed with NSTEMI (n=12). Two patients (2/14) received emergency revascularization. None of these patients died within 30 days. Table 6 displays further details about the patients with HEART scores 0-3 diagnosed with MACE at 30 days. One patient presented with an initially normal ECG that later changed to ST-elevation, and underwent emergency revascularization.

Table 6. Details about the patients with HEART scores 0-3 diagnosed with MACE at 30 days.

	STEMI* (n=1)	NSTEMI (n=12)	PCI (n=2)
History			
Slightly or non-suspicious	1	6	1
Moderately Suspicious	0	5	1
Highly Suspicious	0	1	0
ECG			
Normal	1	12	2
Non significant disturbance	0	0	0
Significant ST-deviation	0	0	0
Age			
18-45 yr	0	4	0
46-64 yr	1	6	1
>=65 yr	0	2	1
Risk Factors			
No risk factors	0	4	1
1-2 risk factors	1	7	1
>= 3 risk factors or atherosclerosis	0	1	0
Troponin			
Less than 99th percentile	0	8	1
1-3 times normal limit	1	3	1
>=3 times normal limit	0	1	0

* This patient had a normal ECG on admission that changed later on to ST-elevation

The high-risk population was defined as a HEART score of 7-10 points. Of the 464 patients defined as high risk, 200 (43.1%) had a MACE and 217 (46.8%) met the criteria for the secondary endpoint.

DISCUSSION

The HEART score for chest pain patients in the ED provides the clinician with a reliable predictor of outcome, without complex calculations, and is able to be assessed, once the results of the troponin assay is received, typically within 1 hour after the arrival of the patient[1,2,3]. This score was validated in the large, independently acquired data set of a prospective study in patients with chest pain symptoms in the Asia-Pacific region (ASPECT).

HEART is a diagnostic score that is strong in identifying low-risk patients. It remains a matter of clinical debate what rate of missed diagnosis is acceptable in the setting of suspected ACS[9,12-14]. A low risk of missed adverse events is desirable. In our analysis a negative predictive value for MACE of 98.3 % was achieved with a HEART score ≤3. This defined 28.2 % of the chest pain population as low risk. A risk of MACE of 1.7 %, with a mortality rate of 0%, is a firm basis to omit redundant diagnostic and treatment steps and move into the direction of quick discharge. However, the early direction given by the HEART score should not prevent the treating physicians from further clinical assessment, with serial troponin sampling and ECGs required in some to confirm or reject initial findings. Additionally the HEART score allows identification of high-risk patients with greater accuracy than the TIMI score. HEART score values ≥ 7, occurring in 15.9 % of the patients, were associated with a positive predictive value of 43.1 % for 30 day MACE. The high risk of MACE in these patients may support emergency invasive procedures.

When comparing the HEART score and the TIMI score for risk stratification the HEART score is a major improvement in predicting risk for ACS in patients with chest pain in the ED, with C-statistic of 0.83 (0.81-0.85) for the HEART score versus 0.75 (0.72-0.77) for the TIMI score. The TIMI score is a prognostic score that was designed about 15 years ago for use in patients with a confirmed ACS, in order to identify those who benefit most

from aggressive anti-clotting agents[5]. It is calculated using binary choices, ignoring the fact that many variables have a 'grey area'. The TIMI score does not classify patient history (anamnesis), even though key guideline state that: "The leading symptom that initiates the diagnosis and therapeutic decision making process is chest pain."[10]. History is of less importance after the diagnosis ACS has been made. The use of the TIMI score for risk stratification of chest pain patients in the ED has been assessed and has been shown to be often not robust in determining patient disposition[4,11-15].

The current study was the largest and most independent validation of the HEART score. Despite some differences in terms of end point definitions and study populations, the current study in the Asia-Pacific region and both previous multicenter validation studies in The Netherlands[2,3] are remarkably similar in terms of patient characteristics and outcome. All studies showed the desired relationship between score and outcome. A retrospective study in the USA also reported a risk of MACE of 0.6% in patients with HEART scores 0-3[16].

Our study has limitations. The ASPECT database was set up in a prospective manner, but it was not designed for testing the HEART score. We classified features of the presenting symptoms to provide the patient history component of the HEART score. Even with this strategy, the history classification was a significant predictor of MACE outcomes. Advantages of the ASPECT population were the prospective nature of the study and the independent data acquisition without any knowledge of the HEART score. Patients with STEMI were not recruited for this trial potentially explaining the moderate MACE frequency in the cases with high HEART scores. This is reflected by the s-shaped curve (figure 2).

MACE was redefined for this study to align closely with the original HEART validation studies. The ASPECT study, designed specifically for recognizing patients who could be safely discharged early, also included ventricular arrhythmia and high-level AV-block as MACE endpoints. These were not included in this study. As the focus of this validation study was to assess the predictive value of the HEART score for ACS, the new MACE definition included NSTEMI, STEMI, urgent PCI or CABG and

death. The defined end point was determined at 30 days, and not 6 weeks as in the original HEART score.

The definition of ACS without ST-segment elevation is composed of relative arguments[10, 17]. Studies are hampered by non-exclusive definitions of unstable angina and NSTEMI. Additionally the causal relationship between the index chest pain presentation and consecutive events is not clearly defined. Both an ACS without MACE and a MACE without ACS may occur in patients with chest pain. No study can isolate and thus describe the true incidence of both situations. MACE is a 'hard' endpoint that acts as an objective indicator of ACS for academic purposes. It does not replace a clinical diagnosis that is subjective by nature.

In conclusion, utilization of the HEART score provided excellent determination of risk for 30-day MACE, comparing well with the TIMI score. This study externally validates previous findings that the HEART score is a powerful clinical tool in this setting. Within one hour from presentation, it identifies both (i) a large proportion of low-risk patients, in whom early discharge without additional testing goes with a risk of MACE of only 1.7%, and (ii) high-risk patients who are potential candidates for early invasive strategies.

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Chapter 7

Occurrence of MACE and death in three validation studies for the HEART score for chest pain patients at the emergency department

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ABSTRACT

Background: The HEART score for the early risk stratification of patients presenting to the Emergency Department (ED) with chest pain contains five elements: History, ECG, Age, Risk factors and Troponin. Each of these may be scored with 0, 1 or 2 points. The purpose of this study was to compare the results of three studies, and analyze possible differences, including a detailed mortality analysis.

Methods: Data of three validation studies with a total of 6226 patients were combined and compared. Study A was a pilot, included in study B. Study B was a retrospective study in 880 patients at four sites in The Netherlands. Study C was a prospective study in 2388 patients at ten sites in the Netherlands. Study D was a prospective study in 2906 patients at 14 sites in nine countries in the Asia-Pacific region. The primary end point of the combined study was the occurrence of major adverse cardiac events (MACE) and death (unless clearly non-cardiac) within four weeks.

Findings: The three studies were comparable in terms of base line characteristics and the risk of MACE and death in various groups of patients. About one third of the chest pain patients had a score ≤3, with a risk of MACE of 1.9% and a risk of death (unless clearly non-cardiac) of 0.05%. In the intermediate risk group (HEART scores 4-6) the risk of MACE was 13.7% with a mortality rate of 0.1%. Patients with HEART scores 7-10 had a risk of MACE of 49.6% and 2.8% of the patients died.

Interpretation: The three validation studies for the HEART score yielded similar results. The event rate in low risk patients is low enough to consider quick discharge without further testing. Those patients with an intermediate score had an event rate that indicates further investigations. High HEART scores correlate with increasing risks of MACE and death, thus supporting aggressive investigation and management.

INTRODUCTION

Chest pain is a common complaint in patients presenting to the Emergency Department (ED). Although the majority of such patients suffer from non-cardiac discomfort, a key differential diagnosis is an acute coronary syndrome (ACS), with the associated high risk of death in untreated patients and the significant reduction of this risk by means of specialized directed therapies[1].

The HEART score was designed for the early risk stratification of patients presenting to the Emergency Department (ED) with chest pain[2,3]. It contains five elements: History, ECG, Age, Risk factors and Troponin. Each of these may be scored with 0, 1 or 2 points. The composition is given in table 1. The application of the HEART score has two purposes. Firstly to identify low-risk patients in whom cardiology diagnostics may be omitted and secondly the identification of high-risk patients in whom directed treatment may be started rapidly.

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

The HEART score was validated in three separate studies[4,5,6]. The purpose of this study was to compare the results of these studies and to analyze possible differences, and to perform a detailed mortality evaluation.

METHODS

The validation program started in 2007 with a retrospective pilot study (study A) in 122 patients with chest pain presenting to the Emergency Department (ED) of one single hospital during the first quarter 2006[2]. This population was incorporated later on in the retrospective study B that is presented next.

Study B was a retrospective study of a consecutive, complete series of 880 chest pain patients presenting to the ED of four participating hospitals in The Netherlands during the first quarter 2006[4].

Study C was a prospective study in 2388 patients at 10 hospitals in The Netherlands[5]. The patient inclusion period lasted from October 2008 to November 2009.

Study D was a study in 2906 patients who were part of a prospective registry at 14 hospitals in 9 countries in the Asia-Pacific region[6]. Overall enrolment for this data set analysis occurred between November 2007, and December 2010, but individual sites started and finished at different times according to local logistics.

A comparison between the designs of the three studies is given in table 2.

Table 2. Comparison of the three validation studies for the HEART score

	Study B	Study C	Study D
Design	Retrospective	Prospective	Prospective
Countries	The Netherlands	The Netherlands	9 countries in the Asia-Pacific region
Hospitals	4	10	14
MACE definition	AMI, revascularization, all cause death	AMI, revascularization, stenosis managed conservatively, all cause death	AMI, revascularization, death unless clearly non-cardiac
Timing of end point	6 weeks	6 weeks	4 weeks

Inclusion period	January 2006 – March 2006	October 2008 - November 2009	November 2007 – December 2010
N patients	880	2388	2906

HEART score criteria

The HEART score was calculated on admission data only. The elements were defined as follows.

History. Patient history was classified according to a mutually agreed distinction between elements of typical or atypical angina. Patients were categorized with typical pain if they presented with central or left sided chest pain with or without radiation to the arms or throat and with or without sweating or clamminess. Patients were categorized with atypical pain if they presented without chest pain or with right-sided chest pain or pain that radiated to the back or worsened on inspiration or palpation. Within the HEART score, 0 points were given for patients with atypical pain only, 1 point when the patient had elements of both typical and atypical pain and 2 points when the patient had typical pain only.

ECG. With regards to ECG findings, 0 points were given if the ECG was normal or had non-specific ST-T wave changes, 1 point was given if it was abnormal but not diagnostic of ischemia (e.g. bundle branch block and pacemaker rhythm) or if there was evidence of pre-existing changes of ischemia or previous infarction, 2 points were given if there were findings of infarction or ischemia not known to be old or consistent with an acute myocardial infarction.

Age. 0 points were given if the patient was younger than 45 years at the time of admission, 1 point if the patient was 45 to 65 years and 2 points if the patient was 65 years or older.

Risk factors. The number of risk factors for coronary artery disease present in the individual was counted. The following risk factors were taken into account: diabetes mellitus, current or recent (< 90 days) smoker, hypertension, hypercholesterolemia, family history of coronary artery disease, or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke or peripheral arterial disease). If the patient had no risk factors, 0 points were allocated. If the patient had one or two risk factors: 1 point. If the patient had three or more risk factors: 2

points. Two points were also given if the patient had a history of significant atherosclerosis.

Troponin T or I. Levels were measured according to local laboratory standards; details are given in the previous publication[5]. Only the troponin value of the first blood sample taken on arrival was used for the HEART score calculation. An elevated troponin was defined as a value greater than the 99th percentile for the assay, as reported by the manufacturer (www.ifcc.org). If the troponin T or I level on admission was equal to, or less than the 99th percentile 0 points were allocated. If the level was between once and three times the 99th percentile: 1 point. If the level was equal to or higher than three times the 99th percentile: 2 points.

Endpoint classification

The original endpoint definitions are given in our previous publications[4,5,6]. In order to allow a uniform adjudication of the endpoints, a new definition was made, and cases were re-classified if applicable. The new definition included the four-week occurrence of:

i. MACE, consisting of acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) (but not stenosis managed conservatively)
ii. death only (unless clearly non-cardiac).

When adjudicating death, distinction was made between cardiac, non-cardiac and unknown causes of death.

The diagnosis of AMI was based on global taskforce recommendations requiring evidence of myocardial necrosis together with evidence of myocardial ischemia (ischemic symptoms, ECG changes, or imaging evidence)[7]. Necrosis was diagnosed on the basis of a rising or falling pattern of the laboratory cardiac troponin concentrations, with at least one value above the 99th percentile, at a level of assay imprecision near to 10%. If the troponin concentration was greater than the reference range, but no rise or fall was recorded, other causes of a raised troponin concentration were considered by the adjudicating cardiologist. If no clear alternative cause of the troponin rise was apparent, and if the clinical presentation was suggestive of an

acute coronary syndrome, an adjudicated diagnosis of acute myocardial infarction was made.

PCI was defined as any therapeutic catheter intervention in the coronary arteries. CABG surgery was defined as any cardiac surgery that involved an operation of the coronary arteries.

TIMI and GRACE definitions

The TIMI and GRACE score were calculated for studies C and D according to the literature[8,9,10]. The database of study B did not contain the necessary data for the calculation of the TIMI and GRACE scores. The GRACE score was unable to be calculated from data in study D.

Statistics

The original data sets for the three studies were used. Baseline characteristics of the study population were analyzed with conventional group descriptive statistics. Descriptive statistics are given as average +/- SD. The c-statistic was calculated to determine the discriminative power of the HEART score and Chi square analyses were used to generate two-by-two tables for the calculation of sensitivity, specificity, and positive and negative predictive values. Analyses were done with SPSS (version 19.0). Subgroups: men/women, elderly, diabetics

RESULTS

A total of 6226 patients were enrolled in the three studies. Patients had similar age and sex distributions in the three studies (table 3).

The occurrence of MACE is given in table 4. The frequency of MACE in the low-risk group (HEART score ≤3) was 38/1993 (1.9%), in the intermediate risk group (HEART score 4-6) 413/3136 (13.7%) and 518/1045 (49.6%) in the high risk group (HEART score 7-10).

Table 3. Base line characteristics

	Study B	Study C	Study D	Total
Patients (n)	880	2388	2906	6226
Age, Mean (SD)	61.3 ± 15.7	60.6 ± 15.4	60.8 ± 14.7	60.8 ± 15.1
Male, n (%)	521 (57.3%)	1372 (57.5%)	1754 (60.3%)	3647 (58.6%)
Diabetes, n (%)	175 (19.9%)	444 (18.6%)	557 (19.2%)	1176 (18.9%)
Smoker (Current/Recent), n (%)	257 (29.2%)	779 (32.7%)	609 (21.0%)	1645 (26.4%)
Hypercholesterolemia, n (%)	229 (26.0%)	856 (35.8%)	1268 (43.6%)	2353 (37.8%)
Hypertension, n (%)	321 (36.5%)	1034 (43.3%)	1588 (54.6%)	2943 (47.3%)
Family History of Coronary Artery Disease, n (%)	281 (31.9%)	866 (36.3%)	1208 (41.6%)	2355 (37.8%)
History of myocardial infarction, n (%)	180 (20.5%)	379 (15.9%)	626 (21.5%)	1185 (19.0%)
History of CABG, n (%)	73 (8.3%)	243 (10.2%)	221 (7.6%)	537 (8.6%)
History of PCI, n (%)	118 (13.4%)	510 (21.4%)	521 (17.9%)	1149 (18.4%)
History of Stroke, n (%)	85 (9.7%)	112 (4.7%)	283 (9.7%)	480 (7.7%)
History of peripheral arterial disease, n (%)	47 (5.2%)	110 (4.6%)	77 (2.6%)	234 (3.8%)

Table 4. Occurrence of MACE in all HEART groups; n (%)

HEART score	Study B 880		Study C 2388		Study D 2906		Total 6174	
0	0/21	0%	1/55	1.8%	0/8	0%	1/84	1.2%
1	0/53	0%	1/157	0.6%	1/106	0·9%	2/316	0.6%
2	1/105	1.0%	4/295	1.4%	4/263	1·5%	9/663	1.4%
3	2/124	1.6%	9/363	2.5%	15/443	3·4%	26/930	2.8%
4	5/146	3.4%	30/390	7.7%	43/627	6·9%	78/1163	6.7%
5	17/147	11.6 %	52/395	13.2%	71/567	12·5%	140/1109	12.6%
6	23/120	19.2%	89/316	28.2%	101/428	23·6%	213/864	24.7%
7	37/75	49.3%	89/204	43.6%	78/253	30·8%	204/532	38.3%
8	30/48	62.5%	63/133	47.4%	80/140	57·1%	173/321	53.9%
9	23/25	92.0%	39/58	67.2%	34/56	60·7%	96/139	69.1%
10	15/16	93.8%	15/22	68.1%	15/15	100%	45/53	84.9%
Total	**153/880**	**17.4%**	**392/2388**	**16.4%**	**442/2906**	**15·2%**	**987/6174**	**16.0%**

P value from the test for heterogeneity =0.22.

In all three studies there is a very similar relationship between the HEART score and the risk of MACE (figure 1). The three curves have a similar pattern with very low risks in patients with HEART scores 0-3 and a more or less linear increase of the risk up to almost 100% in the patients with the highest scores.

Figure 1. Relationship between the HEART score and the risk of MACE

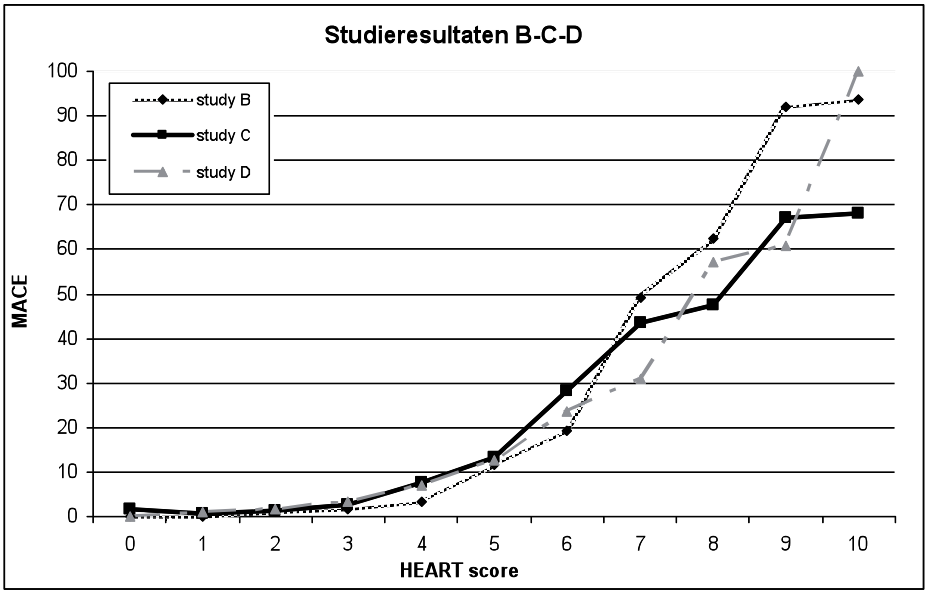

Table 5 outlines the risk of death. Within the low HEART score group two patients died within four weeks. One was a 20-year-old male in study C who committed suicide seven days after presentation. The other case was a 90-year old female in study B with a history of breast cancer, sigmoid resection for cancer, heart failure and atrial fibrillation, who presented with tiredness, shortness of breath and non-specific left-lateral chest pain. An ACS was excluded. This patient died 14 days later due to non-specified reasons. The risk of death (unless clearly non-cardiac) in patients with HEART score ≤ 3 is 1/1993 = 0.05%. In the intermediate risk group (HEART score 4-6) the risk of death (unless clearly non-cardiac) was 4/3136=1.3 % and in the high risk group (HEART 7-10) 29/1045=2.8 %.

Table 5. Occurrence of death (%) in all HEART groups

	Study B	Study C	Study D	Total
	880	2338	2906	6226
HEART	**(n)**	**(n)**	**(n)**	**(n)**
0	0	1*	0	1
1	0	0	0	0
2	0	0	0	0
3	1	0	0	1
4	0	0	0	0
5	0	2	0	2
6	0	2	0	2
7	4	3	0	7
8	4	2	3	9
9	3	2	3	8
10	0	2	3	5
Total	**12 (1.4%)**	**14 (0.6%)**	**9 (0.3%)**	**38 (0.6%)**

* clearly non cardiac

TIMI and GRACE

The c-statistics for the prediction of MACE of the HEART and TIMI scores were calculated. The values for the HEART score were 0.83 in study C and 0.83 in study D. The values for the TIMI score were 0.74 and 0.75, respectively. In addition, the c-statistic of the GRACE score was 0.70 in study C.

Subgroups

The HEART score retained its discriminative ability in diabetics, non-diabetics, females, males, elderly ≥75 years, non-elderly (<75 years), Caucasians and Chinese (table 6).

Table 6. C-statistics in subgroups

	Study B	Study C	Study D
Entire study	0.90 (0.88-0.91)	0.83 (0.83-0.84)	0.83
Diabetics	0.91 (0.89-0.93)	0.79 (0.77-0.81)	0.74 (0.68-0.79)
Non-diabetics	0.90 (0.88-0.91)	0.85 (0.84-0.85)	0.82 (0.79-0.84)
Females	0.91 (0.88-0.94)	0.84 (0.83-0.86)	0.80 (0.76-0.84)
Males	0.89 (0.87-0.90)	0.83 (0.82-0.84)	0.80 (0.78-0.83)
Elderly ≥ 75 y	0.90 (0.86-0.93)	0.74 (0.73-0.76)	0.74 (0.69-0.79)
Non-elderly <75	0.91 (0.89-0.92)	0.86 (0.85-0.87)	0.80 (0.78-0.83)
Caucasians			0.83 (0.80-0.86)
Chinese			0.83 (0.77-0.88)

95% confidence limits are given between brackets.

DISCUSSION

Three multi-centre validation studies for the HEART score for chest pain patients in the ED were combined to strengthen the recommendations for the clinicians and to allow a pooled mortality analysis. The results of the three studies were remarkably similar in terms of base line characteristics, risk assessments and results. In addition, the HEART score retained its discriminative ability in various relevant subgroups. The conclusions were that patients with low HEART scores have a risk of major adverse cardiac endpoints (MACE) of only 1.9% and that at least half of the patients with high HEART scores had MACE. This score may help the clinician in taking treatment decisions in the ED within one hour after their arrival. The event rate in low risk patients is low enough to consider quick discharge without further testing. Those patients with an intermediate score had an event rate that indicates further investigations. High HEART scores support aggressive investigation and management.

The issue of safe discharge of low risk patients was raised by Pope et al[1]. These investigators observed a risk of inappropriate discharge of patients with AMI of 2.1%, in the era before the introduction of troponin assays for clinical use. Mahler et al found a risk of MACE of 0.6% in patients with low HEART scores[11]. Than et al observed a risk of 0.9% in patients with TIMI score 0[12]. Our studies define the cohort of patients with chest pain who may be discharged with a low risk of MACE and death.

According to The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology, an annual cardiovascular mortality of > 2% is deemed high risk, while an annual cardiovascular mortality of <1% is considered low risk, and 1-2% intermediate risk[13].

In this pooled analysis of the HEART validation studies, the risk of MACE was 1.9% in patients with HEART ≤ 3. It should be noted that MACE is used in this setting as a proof of coronary artery disease and not as a sign of poor outcome. Our MACE definition includes revascularizations, which are not 'adverse' in terms of prognosis. The occurrence of MACE does not imply that all patients will automatically end up with an unexpected sudden death. Most patients with MACE heal due to drugs and/or revascularization. The thing that really worries the clinician is sudden death in ACS patients shortly after discharge. In our three validation studies 1993 patients (32.0%) were identified with HEART score ≤ 3, of whom one patient died two weeks later due to a possibly cardiac cause. That single patient determines the risk of death (unless clearly non-cardiac) in the low-risk group of 0.05%.

Limitations

This combined analysis includes one retrospective and two prospective studies. Objections to retrospective studies include the possibility of investigator's bias due to the calculation of the HEART score and the classification of endpoints from the same patient charts. We believe this bias is minimal with hard data such as ours. Retrospective studies have the major advantage of ensuring a complete consecutive series of patients analyzed without selection bias. Indeed, study B shows the (expected) leveling off in the upper part, thus composing the ideal s-shaped

curve as depicted in Figure 1. Prospective studies may not have investigator's bias, but may be influenced by selection bias. In our prospective studies (in particular study C), residents at the ED were requested to fill out a Case Report Form (CRF) for patients with chest pain. Clinical demands may have resulted in patients not being recruited. This practice may have resulted in selection bias. As becomes clear from Figure 1 the curves for the prospective studies C and D don't level off at the near 100% end, raising the possibility of both prospective studies not including all high-risk patients. When pooling retrospective and prospective results the true picture may be obtained.

Conclusion

One retrospective and two prospective validation studies for the HEART score yielded almost identical results. A low HEART score indicates a low risk of MACE and a very low risk of death. It is questionable whether additional assessment is required in patients with a HEART score ≤3. Increasing HEART scores correlate with an increasing risk of MACE and death, thus supporting aggressive investigation and management of high-HEART score patients.

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Chapter 8

Prognostic factors in chest pain patients: a quantitative analysis of the HEART score

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ABSTRACT

Background. Risk stratification for chest pain patients at the emergency room is recommended in several guidelines. The HEART score is based on medical literature and expert opinion to estimate the risk of a major adverse cardiac event (MACE). We aimed to assess the predictive effects of the five HEART components and to compare performances of the original HEART score and a model based on regression analysis.
Methods and results. We analyzed prospectively collected data from 2388 patients, of whom 407 (17%) had a MACE within 6 weeks (AMI, PCI, CABG, significant stenosis with conservative treatment and death due to any cause). Univariate regression analysis showed the same ordering of predictive effects as used in the HEART score. An adjusted score was based on multivariable logistic regression analysis (HEART-adj), which showed slightly better calibration and discrimination (c-statistic HEART 0.83, HEART-adj 0.85). In comparison to HEART, HEART-adj proved in a decision curve analysis clinically useful for decision thresholds over 25%. Nevertheless, the original HEART classified patients better than HEART-adj (NRI=14.1%).
Conclusion. The previously chosen weights of the five elements of the HEART score are supported by multivariable statistical analyses, although some improvement in calibration and discrimination is possible by adapting the score. The gain in clinical usefulness is relatively small and supports the use of either the original or adjusted HEART score in daily practice.

INTRODUCTION

The most common reason for admitting patients to the cardiac emergency room is chest pain[1,2]. The focus of the diagnostic process at the emergency room is to identify both patients who can be safely discharged and those who should be treated aggressively for an acute coronary syndrome (ACS). Definite diagnostic criteria for ACS are lacking[3] and, although approximately 80% of chest pain patients have no clear ACS at presentation[4], clinicians tend to admit patients with ambiguous chest pain for further diagnostic testing or treat them as ACS patients. Consequently, over diagnosis and unnecessary treatment occur frequently and patient burden and costs increase.

Guidelines recommend the use of risk scores for the diagnosis and treatment of non-ST-elevation ACS[3]. In light of these recommendations, we designed the HEART score, given in table 1, to improve risk stratification of chest pain patients at the emergency room without overt ACS at presentation. The score was based on medical literature and expert opinion and included five components of clinical judgment. HEART is an acronym of its components: History, ECG, Age, Risk factors and Troponin. By appreciating each of these five elements with weights of 0, 1 or 2, each patient will receive a score between 0 and 10. The HEART score is applied to identify patients with a high or low risk of MACE within 6 weeks as proof of ACS.

In previous studies discrimination of HEART was very good[5, 6, 7].

In absence of empirical data, the HEART score could not be developed according to standardized methods[8, 9]. The most objective method for model derivation is through statistical analysis of a large cohort of patients, particularly to obtain estimates of strength of different predictive effects. Nevertheless, HEART showed good discriminative ability in two retrospective evaluations[5, 6] and a multicenter prospective study[7].

Since the HEART score was designed in the absence of statistical analysis of empirical data, our aims were to assess the predictive effects of the five HEART components in patient data of our multicenter prospective study and to compare the performance of a model based on regression analysis with the performance of the original HEART score.

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

METHODS

Patient population

Patients were prospectively included at ten hospitals in the Netherlands (see appendix). The patient inclusion period lasted from October 2008 to November 2009. Consecutive patients admitted to the (cardiac) emergency room due to chest pain were eligible irrespective of age, pre-hospital suspicions and previous medical treatment.

Since patients with chest pain and significant ST segment elevations on the ECG during transportation were immediately taken to the nearest catheterization laboratory, these patients did not visit the emergency room and consequently were typically not included in the study. However, some exceptional patients (0.7%) with sudden onset ST-elevation acute myocardial infarction (STEMI) did reach the emergency room, and consequently were included in this study.

Data acquisition and management

Emergency room residents recorded initial patient data on the admission Case Report Form (CRF), before any diagnosis was made. These data consisted of classical elements of patient history, cardiovascular risk factors, medication, physical examination and past medical history. At the time of admission, laboratory values, including cardiac troponin I or T levels were collected and patients underwent ECG.

The HEART score

The HEART score contains five components (Table 1). Each component is divided in three categories with 2, 1 and 0 points.

History. a) The history contains mainly suspicious elements for coronary ischemia, such as middle or left sided, heavy chest pain, initiated by exercise or emotions, radiation and/or relief of symptoms by sublingual nitrates. b) The history contains both non-specific and suspicious elements. c) The history contains no specific elements for coronary ischemia.

ECG. The ECG was taken at the emergency room and categorized according to Minnesota criteria[10]. a) Significant ST-segment depressions or elevations or negative T waves in absence of a left bundle branch block, pacemaker rhythm, left ventricular hypertrophy, or the use of digoxin. b) Repolarization abnormalities without significant ST-segment depressions or elevations or presence of a left bundle branch block or pacemaker rhythm, typical abnormalities indicative of left ventricular hypertrophy, repolarization abnormalities probably caused by digoxin use or in case of unchanged known repolarization disturbances. c) Normal ECG.

Age. Age was categorized as: a) 65 years or older at the time of admission b) 45 to 65 years and c) younger than 45 years.

Risk factors. The following risk factors were taken into account: current diabetes mellitus, current or recent (< 90 days) smoker, hypertension, hypercholesterolemia, family history of coronary artery disease, obesity (BMI > 30). Risk factors were categorized as: a) Three or more risk factors for atherosclerosis, or a history of significant atherosclerosis (coronary revascularization, MI, stroke or peripheral arterial disease) irrespective of the risk factors for

coronary artery disease. b) One or two risk factors. c) No risk factors at all.
Troponin T or I levels were measured according to local standards and categorized as: a) Troponin level on admission higher than three times the local threshold for positivity. b) Troponin level between once and three times the threshold for positivity. c) Troponin level below the threshold for positivity.

Data of a retrospective study [ref n=880] were used to assess the risks of MACE that are related to the HEART scores. The predicted logodds of MACE within 6 weeks of an individual patient equals the individual HEART score minus a constant (7.15). This means that the predicted risk of MACE = 1/ (1-(exp(HEART score - 7.15))).

Follow-up and outcome

The outcome in this study was the occurrence of a major adverse cardiac event (MACE), within six weeks of initial presentation. MACE consisted of: AMI, PCI, CABG, significant stenosis with conservative treatment and death due to any cause.

Data analysis

Predictor effects

Logistic regression analysis was performed with MACE within 6 weeks as outcome. The effects of the HEART predictors were assessed univariably and multivariably. The continuous predictors age and troponin were studied for non-linear relationship with restricted cubic splines[8]. The logistic regression coefficients were used to update the points of the original HEART score.

Validation

The original HEART score and the updated HEART score were applied to all individual patients to calculate the risk of MACE. Observed outcomes were compared with the predicted risks of MACE. Model calibration was assessed by means of calibration plots[11]. Discrimination was quantified with the area under the receiver operator characteristic curve (equal to the c-statistic in case of a dichotomous outcome)[12].

Clinical usefulness was assessed by using decision curve analyses[13].These analyses estimate a 'net benefit' for prediction models by summing the benefits (true positive MACE) and subtracting the harms (false-positive MACE). The latter are weighted by a factor related to the relative harm of a missed MACE versus an intervention. The weighting is derived from the threshold risk of MACE at which a patient would be admitted. This threshold can vary from patient to patient. We concentrated on the net benefit for threshold probabilities between 1% and 50%. This implies a weight of 99:1 for the 1% threshold, and 1:1 for the 50% threshold for missing MACE versus unnecessary admission. The interpretation of a decision curve is that the model with the highest net benefit at a particular threshold risk should be chosen. We compared the adjusted HEART score (HEART-adj) with HEART. Reference strategies were admitting all patients or sending all patients home.

Performance of the original and HEART-adj were further compared my means of reclassification. Reclassification was assessed by cross-tabulating the classification according to the original HEART versus HEART-adj, separately for patients with MACE and without MACE. We estimated the net reclassification improvement (NRI) with the previously proposed cutoff for HEART of 2.5% and 40% risk[14].

Statistical analyses were performed with R (Version 2.9; The R foundation for Statistical Computing, Vienna, Austria)[15] and SPSS 17 (IBM Corporation, NY, USA).

RESULTS

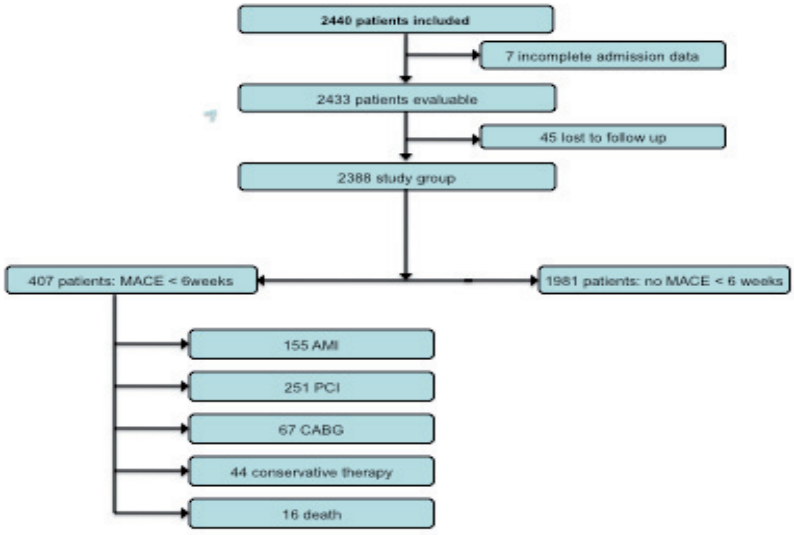
Study population

A total of 2440 patients were included. Seven patients (0.3%) were non-evaluable due to invalid data on admission. In another 45 cases (1.8%) the 6-week follow up was incomplete.

The patient flow is given in appendix.

The study population consisted of the remaining 2388 patients of whom 407 (17%) developed a MACE within 6 weeks. Patient characteristics are given in Table 2. Fifty eight percent of the patients were men; the mean age was 61 years.

Figure 1. Patient flow of the study.



AMI = acute myocardial infarction. CABG = coronary artery bypass graft. PCI = percutaneous coronary intervention. MACE = major adverse coronary events.

Table 2. Patient characteristics

	N (% or SD)
Study group	2388 (100)
Age*	60.6 (15.4)
Male gender	1372 (57.5)
Systolic blood pressure*	141.4 (24.3)
Diastolic blood pressure*	78.1 (21.9)
Diabetes Mellitus	444 (18.6)
Smoker	779 (32.7)
Hypercholesterolemia	856 (35.8)
Hypertension	1034 (43.3)
Family History	866 (36.3)
Obesity	582 (24.4)
History of AMI	379 (15.9)
History of CABG	243 (10.2)
History of PCI	510 (21.4)
History of Stroke	112 (4.7)
History of peripheral arterial disease	110 (4.6)
Troponin#	1.0 (0.1-30)
MACE within six weeks	407(17.0)
AMI	155 (6.5)
PCI	251(10.5)
CABG	67(2.8)
Significant stenosis	44(1.8)
Death	16(0.7)

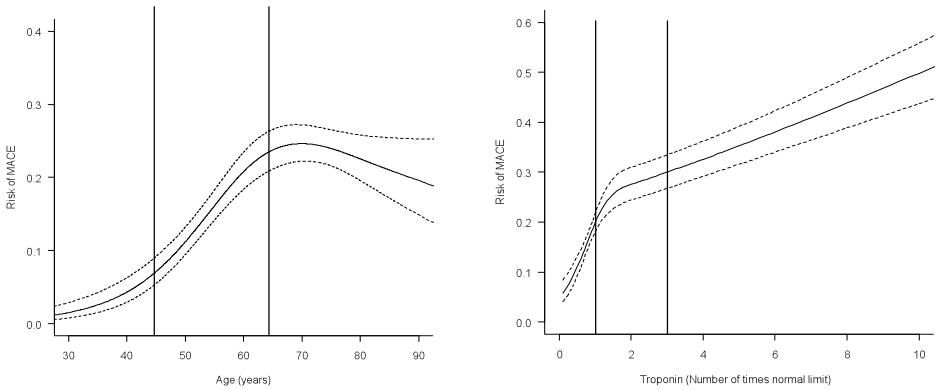
*Mean (SD)
# Median (range)
AMI = acute myocardial infarction. CABG = coronary artery bypass graft. PCI = percutaneous coronary intervention.

Predictor effects

The univariate regression analysis showed the same ordering of predictive effects as used in the HEART score. Higher scores according to HEART corresponded with higher regression coefficients. For example the score for History is 0 – 1 – 2 in the original score corresponded to regression coefficients of 0 – 1.5 – 2.7. The relative weights for each predictor could be calculated as the ratio of regression coefficient (HEART score=2) / regression coefficient (HEART score=1). The relative weight for history is hence 2.7/1.5 = 1.8, which is very similar to the HEART score of 2. Relative weights for the predictor values with HEART score 2 varied between 1.3 and 2.4. Particularly the weight for age was

closer to 1 (1.3). This result can be explained by the form of the association of age and risk of MACE (Figure 2A). The effect of age in patients older than 65 year was relatively small. In contrast, the risk of MACE was higher for patients with higher troponin levels (Figure 2B), which agrees with the relative weight of 1.8 for troponin values higher than 3 times normal level.

Figure 2. Univariate association of age and troponin.



This figure shows the shape of the association of age and troponin with the risk of MACE, after univariate regression analysis. Dotted lines represent 95% CI. The vertical lines are the cutoffs used in the original HEART score.

The multivariable logistic regression analysis provides not only the weights within a predictor, but also corrected for the correlation between different predictors in the model (Table 3). In general, the ordening as used in HEART remained; only for age the highest risk category (age above 65 years) did not show the highest regression coefficient.
Based on the multivariable regression analysis we adjusted the scores of the original HEART, labelled “HEART-adj” (Table 4). Scores were calculated as regression coefficients multiplied by 2 (HEART-adj). The adjusted score shows that some predictor values have different effects than in the original HEART score. A highly suspicious history is scored much higher than for example higher age or multiple risk factors. The predictive effects of Age and presence of risk factors were very similar for the “intermediate” and “high” categories. Age and risk factors are related to each other so that in a multivariable analysis the predictive effects are weakened.

Table 3. Univariate and multivariable logistic regression analyses

	N (no MACE)	N (MACE)	Regr Coeff (SE) Univariate	Regr Coeff (SE) Multivariable
H = 0	902 (46%)	35 (9%)	0	
H = 1	617 (31%)	110 (27%)	1.5 (0.20)	1.27 (0.21)
H = 2	462 (23%)	262 (64%)	2.7 (0.19)	2.06 (0.20)
E = 0	1323 (67%)	147 (36%)	0	
E = 1	380 (19%)	86 (21%)	0.7 (0.15)	0.35 (0.17)
E = 2	278 (14%)	174 (43%)	1.7 (0.13)	1.04 (0.15)
A = 0	376 (19%)	15 (4%)	0	
A = 1	862 (44%)	171 (42%)	1.6 (0.28)	1.24 (0.31)
A = 2	743 (37%)	221 (54%)	2.0 (0.27)	1.12 (0.31)
R = 0	221 (11%)	20 (5%)	0	
R = 1	729 (37%)	116 (28%)	0.6 (0.25)	0.33 (0.31)
R = 2	1031 (52%)	271 (67%)	1.1 (0.24)	0.49 (0.29)
T = 0	1825 (92%)	218 (53%)	0	
T = 1	89 (5%)	55 (14%)	1.6 (0.19)	1.17 (0.21)
T = 2	67 (3%)	134 (33%)	2.8 (0.17)	2.26 (0.18)

MACE = Major Adverse Cardiac Events. Regr Coeff = regression coefficient. SE = Standard Error. H = History, E = ECG, A = Age, R = Risk factors, T = Troponin.
* weights were calculated as regression coefficient/regression coefficient for score=1

Table 4. Comparison of models

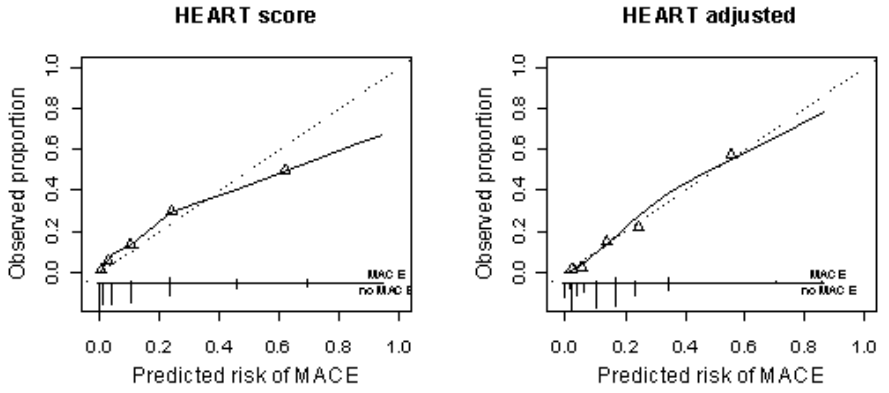
	HEART	HEART-adj (multiplied by 2)
H	0 1 2	0 3 4
E	0 1 2	0 1 2
A	0 1 2	0 2 2
R	0 1 2	0 1 1
T	0 1 2	0 2 5
Max	10	14
c-stats	0.832	0.851

Calibration and discrimination

Calibration of the original HEART score was particularly good for predicted risks of MACE below 50% (80% of all patients) as shown in Figure 3A. Discrimination of the HEART score was good (c-statistic=0.83).

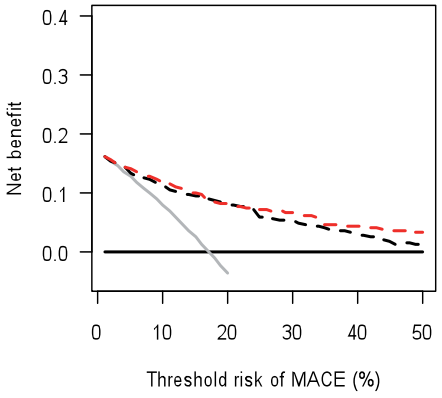
Calibration improved for higher predicted risks, when predictions of MACE were based on the estimated regression coefficients (Figure 3B). Discrimination of HEART-adj was slightly better than HEART (c-statistic=0.85).

Figure 3. Calibration plots of the HEART score and HEART adjusted.



Ideally observed proportions and predicted risks are identical (dotted line). Triangles (Δ) represent patient groups in quintiles. Spikes at the bottom of the graph show the distribution of predicted risks by outcome (MACE yes/no).

Figure 4



Decision curve for the predicted risks of MACE for the original and adjusted HEART scores.

Clinical usefulness

The net benefit, as shown on the y-axis, was similar for HEART and HEART-adj up to 25% risk of MACE. For higher risks, HEART-adj showed higher net benefit (Fig. 4).

We also estimated the net reclassification improvement (NRI) with the proposed cutoff values for HEART of 2.5% for low risk patients and 40% for high risk patients (Table 5).

As shown in table 5 the original HEART resulted in better classification for patients with MACE in 81 (4+77) compared to 30 (7+23) patients better classified by HEART-adj. Thus 81-30=51 patients were netto better classified by the original HEART score.

For patients without MACE, HEART resulted in better classification for 226 (220+6) patients compared to 194 (61+133) patients better classified by HEART-adj (netto 32 patients). As a result, NRI = 51/407+32/1981=14.1% in favour of the original heart score.

Table 5.

HEART	HEART adjusted		
	0 - 3	4 - 9	10 – 14
Patients with MACE			
0 - 3	8	**7**	0
4 - 6	**4**	156	**23**
7 - 10	0	**77**	132
Patients without MACE			
0 - 3	635	**220**	0
4 - 6	**61**	851	**6**
7 - 10	0	**133**	75

The original Heart score was categorised in score values 0 – 3 / 4 – 6 / 7 – 10, related to predicted risks of 0 – 1.6 / 4.1 – 24 / 46 - 95
The adjusted Heart score was categorised in score values 0 – 3 / 4 – 9 / 10 – 14, related to predicted risks of 0 – 2.6 / 4.2 – 35 / 47 - 87

DISCUSSION

To assist the clinician in identifying low risk as well as high risk chest pain patients the HEART score was developed based on clinical experience and literature. The aim of this study was to compare the original HEART score with a model derivation based on logistic regression analysis. Univariate analysis of the five elements showed that the relative weights of the elements were similar to the ones chosen in the original HEART score, with the exception of age. Above the age of 45 years, all patients carry a more or less similar risk and there is no distinction between intermediate and high risk patients.

However, multivariable analysis showed that the relative weights of the elements are somewhat different. History, ECG and Troponin are strong predictors of short-term cardiovascular events while Age and Risk factors make almost no distinction between intermediate or high risk patients. Not surprisingly, older patients have more risk factors for cardiovascular diseases and therefore both predictors highlight the same risk profile.

The newly developed model based on multivariable regression analysis (HEART-adj) and follows empirical data. When comparing HEART-adj with the original HEART score, it shows that calibration is better for the HEART-adj. The higher c-statistic for HEART-adj indicates a better discriminative ability of patients with and without MACE within six weeks compared to the original HEART score. Further, HEART-adj proved clinically useful for decision thresholds over 25%.

Another measure to assess clinical usefulness is the net reclassification improvement of patients[16, 17]. With HEART-adj 159 (220-61) non-diseased patients would have been identified as patients with an intermediate risk of MACE (Table 5) and would therefore be admitted to the coronary care unit. The admission of these non-diseased patients would cause unnecessary occupation of hospital beds and associated increase in medical costs. With the population's increasing age and advancing medical techniques, healthcare costs are a critical issue in many countries. Secondly when these patients will be treated as diseased or ACS patients awaiting the final diagnosis during admission, the possible adverse events resulting from medication and diagnostic procedures are another critical issue.

Contrary the original HEART score would have classified 3 (7-4) diseased patients as low risk patients, who might have been sent home from the emergency room incorrectly. When no follow up is planned for these patients they are prone to the risk of an adverse cardiac outcome.

With respect to the patients in the intermediate and high risk categories, the original HEART score categorized patients more often as high than intermediate risk compared to the adjusted HEART score. A total of 127 (133-6) additional patients without MACE were classified as high risk by the original HEART score compared to intermediate risk according to HEART-adj. These patients will be incorrectly admitted to the coronary care unit and might be treated with medication such as anti clotting agents or intravenous nitrates or undergo a coronary angiography. Secondly compared to HEART-adj, the original HEART score identifies 54 (77-23) patients with a MACE as intermediate instead of high risk patients. These patients who would benefit most from early aggressive treatment[18-21] will experience a delay in treatment and may undergo additional tests such as a classical exercise test, advanced ischemia detection or non invasive imaging by means of multi slice CT scan.

Limitations

In absence of a gold standard for the diagnosis ACS, we chose MACE as a widely applied but not 'undisputed' sign of ACS. An arbitrary six-week follow up period was chosen, as events occurring within this time window are believed to be the result of an index ACS. However, MACE is not more than a useful sign of an ACS for study purposes and not a replacement of a clinical diagnosis.

Remarkably enough, in the HEART score, age is a rather weak predictor of MACE. On the contrary, age is the strongest risk indicator of poor outcome in other risk scores for critically ill cardiovascular patients such as TIMI, GRACE, and PURSUIT[22-25]. The explanation of the difference is probably in the composition of the HEART study population, which is relatively healthy and young and reaches an end point in only 17% of the cases.

Conclusions

The arbitrarily chosen weights of the five elements of the HEART score leave room for improvement by means of adapting the score based on multivariable regression analysis. However, the improvement is relatively small with more patients categorized in the intermediate risk group. Application of the adjusted HEART score will lead hence to more medical consumption in non-diseased patients. Also a small fraction of diseased patients may receive urgent treatment earlier, rather than a period of observation and ischemia detection, when the adjusted HEART score is applied. This analysis supports the easy-to-use original HEART score in daily practice. The HEART score facilitates communication between doctors as it provides all crucial information that can place patients into low, intermediate and high-risk groups for clinically important adverse cardiac events.

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Chapter 9

The predictive value of the exercise ECG for major adverse cardiac events in patients who presented with chest pain in the emergency department

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ABSTRACT

Aims. In order to improve early diagnostic and therapeutic decision-making we designed the HEART score for chest pain patients in the emergency department (ED). HEART is an acronym of its components: History, ECG, Age, Risk factors and Troponin. The score is assessed within one hour after the arrival of the patient. Many chest pain patients undergo exercise testing on the consecutive days after presentation. However, it may be questioned how much diagnostic value the exercise ECG adds when the HEART score is already known.

Methods. A prospective validation study of the HEART score was conducted in ten hospitals, of which four were selected for this sub study. The current analysis concerns 248 patients who underwent cycle exercise testing within 7 days after presentation with chest pain in the ED. The exercise ECGs were reviewed and classified by an adjudication committee, blinded to the HEART score information. The predictive value of exercise testing in terms of major adverse cardiac events (MACE) within six weeks after presentation in the ED is calculated.

Results. In low-risk patients (HEART scores ≤3) 63.1% of the patients had a negative test, 28.6% were non-conclusive and 8.3% had a positive test; the latter were all false positive tests. In the intermediate-risk group (HEART-scores 4-6) 30.9% of the patients had a negative test, 60.3% were non-conclusive and 8.8% were positive, half of these were false-positives. In the high-risk patients (HEART scores≥7) 14.3% had a negative test, 57.1% were non-conclusive and 28.6% were positive, half of these were false-positives.

Conclusion. In a chest pain population, risk-stratified with the HEART score, the exercise ECG has a modest contribution to clinical decision-making. In about half the patients in all risk groups the test is non-conclusive, and the rate of false positive tests is high in all three risk-groups. In intermediate-risk patients, negative exercise tests may contribute to the exclusion of disease. Clinicians should rather go for sensitive tests, in particular in patients with low HEART scores.

INTRODUCTION

The most common reason for admitting patients to the cardiac emergency department (ED) is chest pain [1,2]. In most guidelines and chest pain protocols, the focus is to identify those patients suspected of an acute coronary syndrome (ACS) [3, 4]. In today's practice the majority of the chest pain patients in the ED have no ACS but chest discomfort due to various, relatively harmless causes. However, due to the uncertainties related with suspected ACS, clinicians tend to hospitalize patients with ambiguous chest pain for observation and further diagnostic testing. Many of these patients are treated as an ACS, awaiting the final diagnosis. Consequently, over diagnosis and unnecessary treatment occur frequently and patient burden and cost may be unnecessarily high.

In order to improve diagnostic and therapeutic pathways, we designed the HEART score for chest pain patients in the ED [5]. The HEART score was validated in three multi centre studies [6, 7, 8]. The first was retrospective and yielded promising results [6]. This was followed by the prospective study in 2388 patients at 10 sites from which this is a sub study [7]. The third was an external validation study that was conducted in 2906 patients in the Asia-Pacific region [8]. The conclusions were that patients with low HEART scores have a low risk of major adverse cardiac endpoints (MACE) within four weeks and that the opposite holds true for patients with high HEART scores. This score may help the clinician in taking treatment decisions in the ED within one hour after their arrival.

It is common practice in clinical cardiology to evaluate stable patients by means of exercise testing, as the exercise ECG has a certain predictive value for significant coronary artery stenosis [9]. In addition, the exercise test is applied for patients with unstable chest pain, in particular in the ED setting. According to the ACC/AHA 2002 guideline update for exercise testing, "Use of early exercise testing in emergency department chest pain patients improves the efficiency of management of these patients (and lower costs) without compromising safety." [10]. However, ACS may be caused by endothelial dissection and coronary thrombosis rather than by significant coronary artery stenosis. In addition, ACS prevalence differs between stable outpatients and chest pain patients in the ED. Therefore, sensitivities and specificities of exercise tests are different in stable and unstable patient groups.

As the early risk assessment by means of the HEART score may be translated into a pre-test likelihood this score may provide an attractive setting for exercise test evaluation. The question is: how much adds additional exercise testing to the prediction of MACE when the HEART score is known?

METHODS

Patient population

The prospective validation study of the HEART score was conducted in 2388 patients in ten hospitals in the Netherlands. The ethics committees of all participating hospitals approved the study. As this was an observational non-intervention study, informed consent procedures were waived. However, patients were informed of the registration of data and the follow up policy.

Registrations of exercise ECGs were not part of the original study documentation. For this sub study four hospitals were chosen where complete availability of exercise ECG registrations was anticipated. All documentation of the exercise tests of patients was retrieved either electronically from the electronic patient dossier or photocopied from the paper patient records and kept in the study files. Results of exercise tests were anonymized and separated from other clinical documents for adjudication.

The patient inclusion period lasted from October 2008 to November 2009. Any patient admitted to the (cardiac) ED due to chest pain irrespective of age, pre-hospital suspicions and previous medical treatment was eligible. Since patients with chest pain and significant ST segment elevations on the ECG during transportation were immediately taken to the nearest coronary intervention room, these patients did not visit the ED and consequently, they were not included in the study.

The HEART score

The HEART score contains five components (Table 1). Each component is divided in three categories with 2, 1 or 0 points. ***History***. a) The patient history contains mainly suspicious elements for coronary ischemia, such as middle or left sided, heavy chest pain, initiated by exercise or emotions, radiation and/or relief of symptoms by sublingual nitrates: two points. b) The history contains both non-specific and suspicious elements:

one point. c) The history contains no specific elements for coronary ischemia: 0 points.
ECG. The ECG at rest, taken in the emergency room and categorized according to Minnesota criteria [9], was categorized as follows. a) Significant ST-segment depressions or elevations or negative T waves in absence of a left bundle branch block, pacemaker rhythm, left ventricular hypertrophy, or the use of digoxin: two points. b) Repolarization abnormalities without significant ST-segment depressions or elevations or presence of a left bundle branch block or pacemaker rhythm, typical abnormalities indicative of left ventricular hypertrophy, repolarization abnormalities probably caused by digoxin use or in case of unchanged known repolarization disturbances: one point. c) Normal ECG: 0 points.
Age. Age was categorized as follows. a) 65 years or older at the time of admission: two points b) 45 to 65 years: one point. c) younger than 45 years: 0 points.

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Risk factors. The following risk factors were taken into account: current diabetes mellitus, current or recent (< 90 days) smoker, hypertension, hypercholesterolemia, family history of coronary artery disease, obesity (BMI > 30). Risk factors were categorized as follows. a) Three or more risk factors for atherosclerosis, or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke or peripheral arterial disease) irrespective of the risk factors for coronary artery disease: two points. b) One or two risk factors: one point. c) No risk factors at all: 0 points.
Troponin T or I levels were measured according to local lab standards and categorized as follows. a) Troponin level on admission higher than three times the local threshold for positivity: two points b) Troponin level between once and three times the threshold for positivity: one point or c) Troponin level below the threshold for positivity: 0 points.

The HEART score was calculated on the basis of computer-entered patient data, without subjective interpretations.

Adjudication process

Two cardiologists independent from the hospital where the exercise test was performed reviewed the exercise test. The adjudicators, were unaware of the HEART score or clinical outcome of individual patients. In case of disagreement between two adjudicators the case was discussed in a plenary adjudication committee meeting with at least five members present.

The Case Record Form (CRF) contained entries for: date of birth and test date, use of beta blockers on the day before and/or the day of the exercise test, classification of the baseline ECG, maximal heart frequency, maximal exercise capacity, duration of maximal exercise, maximal blood pressure, symptoms during the test, classification of maximal ECG changes, classification of the technical quality of the test. The CRF contained one section for the personal opinion of the adjudicator on the result of the test: the test could be classified: definitely positive, borderline changes, definitely negative with adequate exercise parameters. A separate entry was given for a an insufficient test if there were no ECG changes but the target heart rate of 90% of the predicted value was not reached. Another separate entry was given for tests with

limited diagnostic value due to significant pre test abnormalities.

Criteria for exercise ECGs

The classification of the exercise ECGs followed the paragraph 'Interpretation of the Exercise Test' of the ACC/AHA practice guidelines [10]. The following criteria for (non-) significant ST segment changes were used. In case of no ST changes the ECG was classified 'unchanged'. In case of ST depressions <1 mm ST or when T inversions occurred the ST-changes were classified 'notable, but insignificant'. In case of upsloping ST depressions with a surface area between the base line and the ST segment > 4 mm^2 was classified 'significant, upsloping'. A new horizontal or down-sloping ST segment ≥1 mm of horizontal or down-sloping ST-segment depression or elevation for at least 60 to 80 milliseconds (ms) after the end of the QRS complex was classified 'significant ST depression'. Other ECG changes (i.e. frequency dependent LBBB, arrhythmias, new ST elevations > 2 mm) were entered in 'miscellaneous other' categories.

Definitions of negative, non-conclusive and positive tests

Classification of the exercise test was based on the ECG as described above. In order to classify a negative test the patient had to have reached ≥ 90% of the predicted value based on age. In case of no or non-significant ECG changes and a maximal heart rate < 90% of the predicted value based on age, the test was classified non-conclusive. In case when the assessment of the ECG during exercise was hampered significantly due to movement disturbances, significant pre-test ECG abnormalities, left bundle branch block, pacemaker rhythm, significant other rhythm disturbances the test was also classified non-conclusive.

Exercise protocols

Standard electrocardiography was applied with paper speed 25 mm/sec and 10 mm/mV. Only cycle ergometers were used. The standard exercise protocol started with 20 Watt and increased with 20 Watt per minute. In some cases the individual exercise protocol was customized to allow 6 to 12 minutes of exercise.

Follow-up and outcome

The outcome measure was the occurrence of MACE within six weeks of initial presentation. MACE consists of: AMI, PCI, CABG, significant stenosis with conservative treatment and death due to any cause.

Data analysis

Statistical analyses were performed with R (Version 2.9; The R foundation for Statistical Computing, Vienna, Austria) [11] and SPSS 17 (IBM Corporation, NY, USA). Calculated variables are given with 95% confidence limits between brackets. Statistical evaluations were performed according to Cook [12]

RESULTS

Study population

The four participating hospitals of this sub study included 767/2388 patients (32.8%) of the entire validation study of the HEART score. Of these 767 patients, 273 had an exercise test (35.6%). Seven of these 273 exercise tests (2.6%) were excluded because the test was performed after coronary angiography, 13 (4.8%) because the test was performed in the setting of myocardial stress imaging, three (1.1%) due to incompleteness of data and two (0.7%) because the exercise test appeared to be performed before the index presentation. The remaining 248 patients (90.8%), who compose the current study population, had an evaluable exercise test, performed before any coronary catheter investigation. The contribution of the four hospitals was: Universitair Medisch Centrum Utrecht (UMCU) (27/105), Gelre Apeldoorn (GA) (69/253), Medisch Centrum Haaglanden Westeinde (MCHW) (72/214), Medisch Centrum Haaglanden Antoniushove (MCHA) (80/182). Eighty-two (33.1%) exercise tests were performed on the day of presentation and the other 166 (66.9%) within 1 week after presentation.

Patient characteristics of the study population and comparisons with the population at the four participating sites and the population of the entire study are given in table 2. In comparison with the population of the entire study, the patients who had an exercise

test were more likely to be male, suffer from hypercholesterolemia, have a positive family history and were more likely to have a history of PCI and CABG.

Table 2. Baseline characteristics

Patient characteristics, N (% or SD)	Patients with an ET	All patients sub study	Entire study
Study group	248	754	2388 (100)
Age*	59.4(13.1)	59.3(16.3)	60.6 (15.4)
Male gender	153(61.7)	420(55.7)	1372 (57.5)
Systolic blood pressure*	146.6(24.0)	145.2(26.2)	141.4 (24.3)
Diastolic blood pressure*	78.8(14.9)	78.0(15.1)	78.1 (21.9)
Diabetes Mellitus	53(21.4)	161(21.4)	444 (18.6)
Smoker	86(34.7)	265(35.1)	779 (32.7)
Hypercholesterolemia	104(41.9)	272(36.1)	856 (35.8)
Hypertension	105(42.3)	305(40.5)	1034 (43.3)
Family History	98 (39.1)	251(33.3)	866 (36.3)
Obesity	56(22.6)	178(23.6)	582 (24.4)
History of AMI	37(14.9)	94(12.5)	379 (15.9)
History of CABG	36(14.5)	82(10.9)	243 (10.2)
History of PCI	61(24.6)	142(18.9)	510 (21.4)
History of Stroke	11(4.4)	39(5.2)	112 (4.7)
History of peripheral arterial disease	12(4.7)	44(5.8)	110 (4.6)
HEART score	4.3(1.8)	4.1(2.1)	4.4 (2.2)
MACE within six weeks	25(10.1)	100(13.3)	407(17.0)
AMI	9(3.6)	39(5.2)	155 (6.5)
PCI	14(5.6)	57(7.6)	251(10.5)
CABG	3(1.2)	21(2.8)	67(2.8)
Significant stenosis	4(1.6)	11((1.5)	44(1.8)
Death	0	6(0.8)	16(0.7)

*Mean (SD)
AMI = acute myocardial infarction. CABG = coronary artery bypass graft. PCI = percutaneous coronary intervention. ET = exercise test

Endpoints

A MACE within six weeks occurred in 25/248 (10.1%) of the patients who had performed a bicycle exercise test. The MACE was an AMI (n=9), PCI (n=14), CABG (n=3) or significant stenosis with conservative treatment (n=4). None of the patients died within six weeks.

Table 3 displays the numbers of exercise tests in each HEART category in each site. An exercise test was performed in 84/308 (27.3%) patients who had HEART scores 0-3 (the low risk group), in 136/345 (39.4%) patients with HEART scores 4-6 (the intermediate risk group) and in 28/101 (27.7%) patients with HEART scores 7-10 (the high risk group).

Table 3. Numbers of exercise tests and total numbers of patients in each HEART score category for each of the participating hospitals.

	Site					
HEART score	**GA**	**MCHA**	**MCHW**	**UMCU**	**Total**	
0	2/6	0/2	1/8	0/5	3/21	(14.3%)
1	1/15	5/24	3/23	1/9	10/71	(14.1%)
2	13/26	12/29	11/40	2/9	38/104	(36.5%)
3	1/30	15/35	12/30	5/17	33/112	(29.5%)
4	14/52	15/31	13/31	6/16	48/130	(36.9%)
5	17/40	19/37	16/36	5/16	57/129	(44.2%)
6	9/32	12/19	8/21	2/14	31/86	(36.0%)
7	7/24	0/1	7/16	5/9	19/50	(38.0%)
8	4/17	2/4	1/8	0/6	7/35	(20.0%)
9	0/8	0/0	0/1	0/2	0/11	(0%)
10	1/3	0/0	0/0	1/2	2/5	(40%)
Total	69/253	80/182	72/214	27/105	248/754	(34%)

GA = Gelre Apeldoorn, MCHA = Medisch Centrum Haaglanden Antoniushove, MCHW = Medisch Centrum Haaglanden Westeinde, UMCU = Universitair Medisch Centrum Utrecht.

Beta blockers

One hundred (40.3%) patients used a beta-blocker on the day of the exercise test and another two patients (0.8%) discontinued a previously prescribed beta-blocker on the day before the test. The drug used was metoprolol in 70.0% of the cases. One hundred thirty-eight patients (55.6%) did not use any beta-blockers at the

time of the exercise test and in eight patients (3.2%) this information was not available.

Pre-test ECG

According to the adjudication committee, pre-test 12-lead ECG was classified 'entirely normal' in 158 patients (63.7%) and borderline, but within normal limits, in 25 patients (10.1%). Thirteen patients (5.2%) had minor repolarization abnormalities (0.05-0.1 mV ST-depression), ten (4.0%) patients had significant ST-depression ≥ 01 mV, typical for ischemia, in at least two contiguous leads, and 32 patients (12.9%) had miscellaneous other ECG abnormalities that may or may not mimic ischemia, such as left ventricular strain, digitalis effect, negative T-waves or a left bundle branch block. The pre-test ECG could not be classified in ten patients (4.0%) for quality reasons.

Performances

The maximum heart frequency was on average 137.1 +/- 26.7 bpm. The maximum exercise performance was expressed in Watts in 228 patients; the average was 133.2 +/- 56.6 Watt. In 19 patients, the exercise was expressed in metabolic equivalents (METS), with an average of 11.4 +/- 3.3 METS. In 1 patient, data on the maximum exercise performance were not available. The duration of the exercise tests was on average 6:11 +/- 2:21 minutes. The maximal systolic blood pressure was on average 192.0 +/- 31.9 mmHg. The maximal diastolic blood pressure was on average 90.6 +/- 24.3 mmHg. Data on blood pressure were incomplete in 3 patients.

Symptoms

Symptoms occurred in 212 patients (85.5%) during the exercise test. Thirty-two patients had chest pain, typically combined with dyspnoea, 180 had other symptoms than chest pain, typically dyspnoea, tiredness or leg discomfort, and 21 patients had no symptoms. In 15 patients, data on symptoms were not available.

ECG during exercise

The technical quality of the ECG recordings was qualified by the adjudication as 'good' in 181 patients, 'reasonable' in 42, 'fair'

in 15 and 'poor' in 10 patients. During the exercise test the ST segment did not change in 149 patients (60.1%). Notable, but non-significant ST changes (0.05 – 0.1 mV ST depression or T inversions) occurred in 59 patients (23.8%). Twenty-six patients (10.5%) had significant, horizontal or down-sloping ST depression >0.1mV and one patient (0.4%) had a significantly abnormal up-sloping ST depression, together composing the group of 27 (10.9%) unequivocal positive tests. In 13 other patients (5.2%) other changes on their ECG were observed, such as frequency dependent left bundle branch block or arrhythmias with secondary repolarization disturbances.

Negative and positive exercise tests

Numbers of negative, border line negative, non-conclusive, borderline positive and positive exercise ECGs in each HEART score category are given in table 4a for patients without MACE and in table 4b for patients with MACE.

Table 4a. Adjudicated results of exercise ECGs in patients without MACE: occurrence of negative, non-conclusive and positive tests in terms of ST-segment changes

	Outcome of exercise ECGs in patients without MACE			
HEART score	Negative	Non conclusive	Positive	**Total**
0	2	1	0	**3**
1	7	2	1	**10**
2	24	10	3	**37**
3	19	10	3	**32**
4	22	22	2	**46**
5	15	32	3	**50**
6	5	19	1	**25**
7	3	9	1	**13**
8	0	3	3	**6**
9	0	0	0	**0**
10	0	1	0	**1**
Total	**97**	**109**	**17**	**223**

Table 4b. Adjudicated results of exercise ECGs in patients with MACE: occurrence of negative, non-conclusive and positive tests in terms of ST-segment changes

	Outcome of exercise ECGs in patients with MACE			
HEART score	Negative	Non conclusive	Positive	Total
0	0	0	0	**0**
1	0	0	0	**0**
2	0	1	0	**1**
3	1	0	0	**1**
4	0	1	1	**2**
5	0	3	4	**7**
6	0	5	1	**6**
7	1	2	3	**6**
8	0	0	1	**1**
9	0	0	0	**0**
10	0	1	0	**1**
Total	**2**	**13**	**10**	**25**

A negative test or borderline negative test occurred in 99/248 (39.9%) of the patients. For further analysis, negative and borderline negative tests are grouped together. Almost half of the patients (49.2%) had a non-conclusive exercise ECG. A positive or borderline positive test occurred in 27/248 (10.9%) of the patients. Also positive and borderline positive tests are grouped together. HEART scores 0-3 were considered ‘low risk’, 4-6 ‘intermediate risk’ and 7-10 ‘high risk’.

Low-risk group

The exercise ECG results for the low-risk-group (HEART≤3) in relation to the occurrence of MACE are given in table 5a.

The negative predictive value (NPV) of the exercise ECG for the occurrence of MACE was 0.981 (0.886-0.999) and the positive predictive value (PPV) was 0 (0-0.439).

Table 5a		Occurrence of MACE		
		No MACE	MACE	**Total**
Exercise ECG	Negative	52	1	**53**
	Non conclusive	23	1	**24**
	Positive	7	0	**7**
	Total	**82**	**2**	**84**

Intermediate-risk group

The exercise ECG results for the intermediate-group (HEART 4-6) in relation to the occurrence of MACE are given in table 5b.

The NPV of the exercise ECG for the occurrence of MACE was 0.736 (0.600-0.840), the PPV was 0.5 (0.222-0.777).

Table 5b		**Occurrence of MACE**		
		No MACE	MACE	**Total**
Exercise ECG	Negative	42	0	**42**
	Non conclusive	73	9	**82**
	Positive	6	6	**12**
	Total	**121**	**15**	**136**

High-risk group

The exercise ECG results for the high-risk-group (HEART≥7) in relation to the occurrence of MACE are given in table 5c.

The NPV of the exercise ECG for the occurrence of MACE was 0.75 (0.219-0.986) and the PPV was 0.5 (0.174-0.825).

Table 5c		**Occurrence of MACE**		
		No MACE	MACE	**Total**
Exercise ECG	Negative	3	1	**4**
	Non conclusive	13	3	**16**
	Positive	4	4	**8**
	Total	**20**	**8**	**28**

DISCUSSION

Exercise testing after HEART score assessment has a modest contribution to the making of a clinical diagnosis. Distinction between low-, intermediate- and high-risk patient groups may provide an answer to the question in which groups of patients the test may be valuable or not.

The low-risk group (HEART score ≤3), which accounts for 33.9% of the study population, holds a 6-week risk MACE of 2.4%. In the light of this low pre test likelihood, additional testing makes sense only when the test has few false-positives. In this case, 8.3% of the patients had a positive exercise test but none of them had a MACE. However, these positive exercise tests have fed the suspicion of a serious cause of the chest pain and consequently to the unnecessary occupation of hospital beds and to medical procedures. Consequently, iatrogenic damage may have occurred. The diagnosis of coronary artery disease was not confirmed in any of the patients with a positive exercise test. Therefore, exercise testing is not recommended in low-risk chest pain patients.

The intermediate-risk group (HEART score 4-6), which accounts for 54.8% of the original study population, holds a 6-week risk of MACE of 11.0%. In the patients with a negative test, MACE did not occur. The majority of the patients (60.3%) had a non-conclusive exercise test due to various reasons, mostly incapability to reach the predicted maximal heart frequency. In this group 11.0% of the patients had a MACE that was not predicted by the exercise test. Twelve patients (8.8%) had a positive test, of which 50% had a MACE. In patients with an intermediate HEART score, the exercise test may be helpful for excluding disease but most patients have a non-conclusive test, which is not helpful for the clinician. The high number of false-positives is a concern.

The high-risk group (HEART score ≥7), which accounts for 11.2% of the original study population, holds a 6-week risk of MACE of 28.6% in this sub study. In the entire HEART validation study, the risk of MACE in the high HEART score group was 50.1%. Clearly, the current subgroup was a selection of doubtful cases after ‘filtering out’ the clear-cut ACS cases. The patients with

a positive exercise test had a risk of 50% to have a MACE. A case could be made for early invasive strategies for all patients with high HEART scores. A consequence of such strategies could be to declare any non-invasive diagnostic work up redundant.

Comparison with literature

According to a recent study by Gaibazzi et al, in chest pain patients with typical ECG changes but without a rise of troponin levels, bicycle exercise tests did not properly predict the risk of developing a nSTE-ACS [13]. Mahler and co-workers stated that if used to guide objective cardiac testing, the HEART score could have substantially reduced cardiac testing in the low-risk HEART score cohort [14]. In the study in patients in a chest pain unit by Gibler et al. a graded exercise test was found to have a sensitivity of 28.6%, a specificity of 99.4%, a positive predictive value of 44.4% and a negative predictive value of 98.7% [15]. Blankstein et al. demontrated that a positive exercise treadmill testing had a limited sensitivity but high specificity for the detection of >50% stenosis by CT angiography [16].

Limitations

The exercise test in cardiology was not designed to predict adverse outcomes in acute chest pain patients, but to diagnose coronary ischemia in stable angina patients. However, the test is widely applied in chest pain populations in order to “add certainty”, in particular before discharging patients with chest pain that is believed to have a non-coronary cause. When additional testing of chest pain patients in the ED is desired, the clinicians should go for sensitive tests. Sensitivity is not the characteristic of the exercise test, as “It is apparent that the true diagnostic value of the exercise ECG lies in its relatively high specificity. The modest sensitivity (about 50%) of the exercise ECG is generally less than the sensitivity of imaging procedures.” [10].

This study reflects clinical practice, not an experimental environment. Routine exercise testing in this population is hampered by various less-than-optimal circumstances for diagnostic purposes, such as the use of beta-blockers in 70% of the cases, concomitant diseases, the setting of clinical medicine and sometimes failing equipment or technicians.

Although the study population was part of a prospective study, the decision to perform an exercise test was left to the clinicians. Therefore, selection bias is apparent. Various reasons for omitting exercise tests may apply and it is not possible to retrieve the true reasons retrospectively. Considerations that may have played a role are for example a lack of reason when a diagnosis has already been made and/or the patient was immediately revascularized, disability of the patient and the non-availability of equipment and technicians.

CONCLUSION

In a chest pain population, risk-stratified with the HEART score, the exercise ECG has a modest contribution to clinical decision-making. In about half the patients in all risk groups the test is non-conclusive, and the rate of false positive tests is high in all three risk-groups. In intermediate-risk patients, negative exercise tests may contribute to the exclusion of disease. Clinicians should rather go for sensitive tests, in particular in patients with low HEART scores.

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Chapter 10

Consumption of diagnostic procedures and other cardiology care in chest pain patients after presentation at the emergency department

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ABSTRACT

Objective. The HEART score serves risk stratification of chest pain patients at the emergency department (ED). Quicker and more solid decisions may be taken in these patients with application of this score. An analysis of medical consumption of 122 acute chest pain patients admitted before the introduction of this score may be indicative of possible savings.
Methods. Numbers of cardiology investigations and clinical admission days have been counted. Charged cost of medicine was divided in three categories: ED, in-hospital, and outpatient clinic.
Results. Total cost of care was € 469.631, with an average of € 3,849 per patient. Seventy-five percent of this cost was due to hospitalization under the initial working diagnosis Acute Coronary Syndrome (ACS). This diagnosis was confirmed in only 29/122 (24%) of the patients.

The low-risk group (41 patients with HEART scores 0-3) included one patient with a previously scheduled CABG. In the remaining 40 patients, hospitalization occurred in 12/40 (30%) patients and 30/40 (75%) patients visited the outpatient clinic. Total cost of medical care after presentation to these 40 patients was € 37.641, without any case where a new diagnosis of coronary artery disease was made. When medical care in this sub group is classified as redundant, and the latter figure is extrapolated to the national situation in 2012, savings of € 32 million annual would be feasible.
Conclusion. When the HEART score would be generally applied, diagnostic pathways could be shortened and cost reduced, in particular in low risk patients.

INTRODUCTION

The acute coronary syndrome (ACS) is a complex of symptoms caused by a –possibly threatening- occlusion of a coronary artery. However, in the majority of the cases chest pain is caused by various other cardiac and non-cardiac conditions[1].

In order to improve risk stratification in chest patients without overt acute coronary syndrome (ACS) at presentation on one hand and to place relative arguments for ACS into perspective on the other hand, we developed the HEART score for chest pain patients at the emergency department (ED)[2]. The score was based on clinical experience and medical literature and designed to be as easy to use as the Apgar score for newborns. HEART is an acronym of its components: History, ECG, Age, Risk factors and Troponin. Each of these may be scored with 0 (symptom absent), 1 (symptom doubtful) or 2 points (symptom present). The HEART score has been validated in various studies.

The first validation study was a pilot retrospective analysis in 122 acute chest pain patients of a single hospital. This study was extended with patient data from three other hospitals to compose the first multi centre validation study in 880 patients[3]. This was followed by a prospective validation study in 10 hospitals in The Netherlands[4]. An external validation study in 2906 patients in 14 hospitals in the Asia-Pacific region is currently in progress[5]. The data of all these studies are remarkably consistent and show both high negative and high positive predicted values for outcome.

As a first step in the implementation process of the HEART score an analysis of medical consumption is made in patients admitted before the introduction of this score. The results may be indicative of possible savings when the score becomes part of clinical decision-making.

METHODS

The study population consists of a complete series of all patients with acute chest pain who presented at the emergency room (ED) of the Hofpoort Ziekenhuis Woerden in the first quarter 2006. Clinical characteristics have been published previously in

the Netherlands Heart Journal[2]. The average age of the patients was 61,2 +/- 15,4 years.
The HEART score was calculated according to table 1. Details of the criteria are given in a previous publication[3].

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

MACE was defined as the six-week occurrence of an acute myocardial infarction (AMI), percutaneous coronary interventions (PCI), coronary arterial bypass graft operations (CABG) and death due to any cause.

The quantification of medical consumption was based on a combination of medical files and complete series of hospital invoices. Both sources were combined into a new data base. Distinction was made for each item whether it had taken place at the ED, cardiology clinic or outpatient clinic. Focus of the investigation was on the cardiology diagnostics. Therefore, invoices for non-cardiology medical care such as consultation

fees for other medical specialists, abdominal echocardiography and microbiology were ignored. Charges from other hospitals after referral of the patient, in particular costs due to treatments such as PCI and CABG were also ignored. The same holds true for drug therapies. Results are given as mean +/- SD.

RESULTS

Clinical admissions

The distribution of the HEART scores and the numbers of MACE in each category are given in table 2. The risk of MACE during six weeks after presentation increased with the HEART score. Twenty-nine of the 122 patients (24%) had a total of 38 MACE.

Table 2. Numbers of patients in each HEART score and the occurrence of major adverse cardiac events (MACE).

HEART score	N patients	AMI	Revascularization		Death	MACE (pts)	MACE (%)
			PCI	CABG			
0	3	0	0	0	0	0	**0%**
1	10	0	0	0	0	0	**0%**
2	16	0	0	1	0	1	**6%**
3	12	0	0	0	0	0	**0%**
4	28	2	2	0	0	3	**11%**
5	20	4	3	0	0	5	**25%**
6	11	3	2	1	0	4	**36%**
7	10	3	3	2	0	7	**70%**
8	7	2	3	0	2	5	**71%**
9	4	2	0	2	0	3	**75%**
10	1	0	1	0	0	1	**100%**
	122	**16**	**14**	**6**	**2**	**29**	**24%**

AMI = acute myocardial infarction. PCI = percutaneous coronary intervention. CABG = coronary bypass graft. MACE = major adverse coronary event.

Seventy-nine of the 122 patients (65%) were hospitalized. This resulted in a total of 567 hospitalization days. Fifty-six patients stayed at the coronary care unit (CCU), with an average length of stay of 2.2 +/-2.6 days. Additional data on numbers of hospitalizations in each HEART category is given in table 3.

Table 3. Numbers of hospitalized patients and hospitalization days at the CCU and the clinical cardiology department in each HEART score.

HEART score	N patients	CCU		Clinic		Total CCU and or clinic		
		Pts	Days	Pts	Days	Pts	% adm	Days
0	3	0	0	0	0	0	0%	0
1	10	0	0	1	4	1	10%	3
2	16	5	17	7	18	7	38%	30
3	12	5	6	7	14	7	50%	18
4	28	13	21	19	75	19	71%	85
5	20	9	10	14	80	15	65%	79
6	11	7	10	9	57	9	73%	55
7	10	7	19	9	99	9	90%	112
8	7	5	15	7	50	7	100%	70
9	4	4	17	3	23	4	100%	39
10	1	1	9	1	21	1	100%	29
Total	**122**	**56**	**124**	**77**	**443**	**79**	**65%**	**567**

CCU = Coronary care unit, adm = admissions

Table 4. Cost in € of presentation, clinic and outpatient clinic

HEART score	N patients	ED	Clinical admission	Outpatient	Total cost	Total per patient
0	3	609	0	0	609	203
1	10	2530	1263	92	3885	386
2	16	4399	34960	3756	43115	2695
3	12	2994	14330	6150	23474	1956
4	28	8558	59061	12632	80251	2866
5	20	5566	43611	11935	61112	3056
6	11	2969	34313	6378	43660	3969
7	10	2613	67605	24573	94791	9479
8	7	1885	40376	10686	52947	7564
9	4	1165	35274	8736	45175	11294
10	1	342	20152	118	20612	20612
Total	**122**	**33630**	**350945**	**85056**	**469631**	**3849**

ED = Emergency Department.

Cost

Charges of the ED, clinic, outpatient clinic and totals are given in table 4. The total cardiology related cost was € 469.631. The mean cost of presentation at the ED was € 276 +/- 108 per patient. The cost of presentation accounts for 7% of the total cost. The cost of clinical observations was € 350.945, accounting for 75% of the total. The clinical charges consist of cost of hospitalizations for 84% and diagnostics, cardiology consultation fees and laboratory investigations for 16%. In 2006, the day charge was € 1.574 for the CCU and € 255 for the clinic. The cost of clinical admission was € 4.442 on average per patient. The total cost of later outpatient visits for all patients was € 85.056, reflecting 18% of all costs, and on average € 1198 per outpatient.

Numbers of cardiology investigations are given in table V.

Table 5. Numbers of cardiology investigations.

HEART score	N pts	Exercise test	Echo	Scinti grafy	Coronary angiography	
					In hospital	After referral*
0	3	0	0	0	0	0
1	10	1	1	0	0	0
2	16	7	2	0	1	0
3	12	5	4	0	1	0
4	28	22	4	1	3	0
5	20	12	11	0	3	4
6	11	6	7	0	2	2
7	10	9	8	0	5	2
8	7	4	5	1	2	1
9	4	1	6	0	0	2
10	1	0	0	0	0	1
Total	**122**	**67**	**48**	**2**	**17**	**12**
Per procedure (€)		**83**	**124**	**950**	**1548**	
Total (€)		**5561**	**5952**	**1900**	**26316**	

PCI = Percutaneous Coronary Intervention. CABG = Coronary Artery Bypass Graft
* Cost after referral not included.

Low-risk group

In the HEART scores 0-3 group, 15/41 (37%) patients were admitted for clinical observation. The observation period consisted of 23 days at the CCU and 28 days at the cardiology clinic. Charges for hospitalization only were € 36.202 and € 9.016, respectively. The total cost of hospitalization plus clinical investigations was € 50.553. The average duration of hospitalization was 3.9 +/- 1 days. The average cost of hospitalization was € 3.370 per hospitalized patient. One patient reached an end point, a CABG occurring a couple of weeks after presentation. The index presentation of this patient was a visit to the ED due to a hematoma after an elective diagnostic coronary angiography. He also reported chest pain due to his previously documented stable angina. Therefore, this case was part of the analysis. The coronary revascularization was already scheduled before the presentation to the ED.

In this low-risk group exercise testing was performed in 13/41 (32%) patients. The total charge for these tests was € 1.079. Coronary ischemia was never diagnosed in any of these tests. An echocardiogram was made in 7/41 (17%) patients, for a total charge of € 868. Myocardial scintigraphy was never done in this sub group. Two of 41 (4%) patients underwent coronary angiography. The cost of these was € 3.168 in total. Neither of these patients had significant stenosis. Thirteen of 41 patients (32%) returned to the outpatient clinic after discharge. The total cost of outpatient care was € 9.998, reflecting € 769 per outpatient.

Intermediate- risk group

In the intermediate risk group, with HEART scores 4-6, 43/59 (69%) patients were observed clinically. The total cost of hospitalization was € 136.985. The observation period was 41 days at the CCU, with a total charge of € 64.534 for cost of hospitalization. In addition, these patients were hospitalized at the cardiology department for 212 days. The cost of hospitalization was € 3.186 per hospitalized patient. The average duration of hospitalization was 5.8 days (SD = 3.4). In this sub group 37/59 (68%) patients had an exercise test, at a total charge of € 3.320. An echocardiogram was made in 21/59 (37%) patients, at a total

charge of € 2.728. In 1/59 (2%) patients a myocardial scintigram was made at a charge of € 950.

Eight of the 59 (14%) patients underwent an elective coronary angiography. The cost of these were € 7.600. In addition, six patients were referred for emergency invasive strategies (cost not included in this analysis). Significant stenosis was seen in 9/14 (64%) patients. In this intermediate risk group, 39/59 (66%) patients visited the outpatient clinic after clinical discharge. The total charges for outpatient care were € 30.945 or € 793 per outpatient.

High-risk group

In the group of patients with HEART-scores 7-10, one patient was immediately referred to the intervention centre elsewhere for emergency invasive treatment. The other 21/22 (95%) patients were admitted for clinical observation. All together, these patients stayed 60 days at the CCU, with a total charge of € 94.446, and 193 days at the clinical cardiology department. A total of € 163.407 was charged for all clinical cost. Clinical cost was € 7.781 per hospitalized patient. The average duration of hospitalization was 12.0 +/- 6.4 days.

Exercise testing was performed in 13/22 (63%) patients, at a total cost of € 1.162. An echocardiogram was made in 13/22 (86%) patients, at a total charge of € 2.356. In one of the 22 patients (5%) myocardial scintigraphy was done, at a cost of € 950. Seven of the 22 patients (32%) underwent elective coronary angiography, at a total cost of € 10.836. In addition, six patients were referred at some point in time for emergency diagnostic and/or therapeutic coronary intervention (cost of these not included). In the high-risk group 18/22 (82%) patients visited the outpatient clinic. The cost of outpatient care was € 44.11, which was € 2.450 per patient.

Discussion

The evaluation of chest pain patients at the ED is complex and requires many diagnostic procedures. The HEART score serves reliable risk stratification, without additional diagnostics within one hour upon arrival of the patient [2,3,4,5]. Therefore, it is

timely to determine what diagnostic pathways may be useful or redundant once the HEART score is known.

This study is an analysis of medical consumption in 122 acute chest pain patients. Seventy-nine of these 122 patients (65%) were admitted for clinical observation under the suspected diagnosis ACS. The diagnosis was confirmed in only 29 of these 79 cases (37%) in terms of the occurrence of at least one MACE. In the remaining 63% of those patients this diagnosis was not confirmed. This fact may be interpreted as over diagnosis in roughly two thirds of these patients.

Reduction of diagnostics

According to generally accepted methodological principles, diagnostic tests do not add any value in case of low pre test likelihood, in particular when the used testing methods result in many false positive and false negative results. Reduction of redundant diagnostics has the potential of reducing iatrogenic damage. In this context iatrogenic damage may consist of complications due to procedures, medication errors, radiation damage, hospital infections and possible traumatic experiences due to the hospital stay. Unfortunately, iatrogenic damage is hard to measure. By means of the measurement of diagnostic consumption we may get an impression what savings can be made for patients and the health care system.

About one third of the patients in our four validation studies have HEART scores 0-3. In these groups the risk of MACE is 1-2%. Classical exercise testing has a sensitivity of only 65-70% and a specificity of 75-80% [6]. Also advanced ischemia detection by means of myocardial scintigraphy, CT-scan and MRI have limited positive and negative predictive values for significant coronary artery disease. Therefore, it is very questionable whether these diagnostic procedures are useful in a setting of a 1% risk.

About half the patients had moderate HEART scores (4-6), indicating a risk of 12-20%. In this setting, the HEART score does not help the clinician very much in choosing the best diagnostic policy, other than the decision to admit the patient for clinical observation and to perform diagnostic procedures.

HEART scores 7-10, indicating risks of MACE up to 100%, occurred in 17% of the patients. This study group is relatively small as the majority of high-risk patients never reach the ED but are immediately transported to the intervention room. As far as these patients do reach the ED, a case may be made for immediate referral to the intervention room.

Savings

A total of € 60.551 has been spent on all kinds of medical costs after presentation at the ED of 41 low risk patients. One of these was the patient with a scheduled CABG before presentation; with a cost of € 22.910. The other 40 patients were evaluated at a total cost of € 37.641, without disease being confirmed in any case. When extrapolating this figure for the entire year 2006, savings of € 150.564 could theoretically have been made in a 265-bed hospital by leaving all diagnostic procedures in low HEART score patients. With 45,000 hospital beds in The Netherlands, this translates into national savings of € 26 millions in 2006. When assuming an annual cost increase of 4%, this implies theoretical savings of over € 32 million in the current 2012 situation.

The cost analysis in patient groups with moderate or high HEART scores does not bring us clear messages. One of the most important observations is that the cost in these patients is dominated by hospitalization in a therapeutic setting such as patients with a myocardial infarction or clinical recovery after CABG.

References

Than et al. made a comparable risk stratification in 3582 chest pain patients at 14 EDs in 10 countries in the Pacific Asian region[7]. In the pacific analysis 9.8% of the patients were predicted to have a low risk. These patients appeared to have a risk of MACE of 0.9%. Than suggested that these patients did not require additional diagnostic procedures, but potential savings were not given in the publication.

Mahler et at applied the HEART score to 1070 pre-selected low risk chest pain patients at the ED of a hospital in the United States of America (USA)[8]. HEART-scores 0-3 implied a risk of

MACE of 0.6% in this study. It was suggested that annual savings of $ 112.000 - 204.000 could be made in a single hospital by reduction of diagnostic procedures in the low-risk group.

Strengths and limitations

The study population concerns patients who were admitted in the first quarter 2006. Consequently, the data are six years old. On the other side, strong aspects are that the clinical data are published, the HEART score did not influence the clinical policy and detailed financial data for all clinical procedures are available. Ever since 2006 cardiology has developed further. Practically all hospitals in The Netherlands dispose today of a specialised Cardiology Emergency Department (Eerste Hart Hulp, EHH). In addition, many sites dispose of equipment for cardiac CT and MRI. In the study of Mahler conducted in 2008-2010 in the USA, (mentioned above), CT scans were performed in one third of the patients[8]. These developments have resulted in further rise of medical consumption, although the diagnostic benefit of the modern diagnostic procedures is not undisputed.

Last but not least, the focus of this analysis was to investigate whether the diagnostic HEART score helps in reducing diagnostic procedures. Therefore, the therapeutic costs were ignored by intention. These occur in particular after referral to specialised centres for cardiac catheter interventions and thoracic surgery. The incidence of such procedures increases with higher HEART scores.

All limitations mentioned above result in relative under estimation of medical consumption in today's practice.

Conclusion

The HEART score is helpful in quickly taking better medical decisions with regards to diagnostic and treatment options for chest pain patients at the ED. In particular in patients with low HEART scores hospital admissions and specific diagnostic procedures may be reduced. When avoiding redundant medical care, iatrogenic damage may be reduced and savings of tens of millions Euros may be made for the national health care system.

Acknowledgements
Words of gratitude are expressed to Elsbeth Klop from the finance department of the Hofpoort ziekenhuis, who supplied the billing history of the patients in this study.

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Chapter 11

Medical consumption in chest pain patients after presentation in the emergency room

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ABSTRACT

Background

Patients with chest pain are often admitted for clinical observation, and treated as an acute coronary syndrome (ACS) awaiting final diagnosis. Consequently, unnecessary diagnostics and treatment are common. The HEART score serves the making of a quick diagnosis and consists of five elements: History, ECG, Age, Risk factors and Troponin.

Accurate risk stratification in chest pain patients in the emergency department (ED) by means of the HEART score, may help to identify low risk patients who do not need additional work-up or hospitalization.

Methods

This sub study was conducted retrospectively in 280 patients in three hospitals in The Netherlands. These patients were selected from the 2388 patients of the prospective validation study of the HEART score. Individual HEART scores as well as occurrence of Major Adverse Cardiac Events (MACE) within six weeks were registered. Numbers of hospitalization days, exercise tests, echocardiograms and various other cardiology examinations were counted.

Results

A total of 102/280 chest pain patients (36.5%) were classified as low-risk (HEART score ≤ 3). MACE did not occur in this study cohort, as compared to a risk of MACE of 15/870 (1.7%) in the low HEART score group of the entire prospective study. Eighteen patients (17.6%) were hospitalized for a total of 28 days and additional cardiology related work-up was done in 52 patients (51%). These included exercise tests (26.5% of the patients), echocardiograms (15.7%) and coronary angiography (4.9%).

Conclusion

If a policy is made to withhold redundant medicine in low-risk chest pain patients (defined by HEART score ≤3), hospitalizations would be saved in one fifth and various examinations in half of these patients. Improved risk stratification in chest pain patients may result in a reduction of medical consumption.

INTRODUCTION

Health care cost in the Netherlands has risen dramatically in the last decade. The predicted total collective expense on health care for 2012 is 64 x 10^9 euro [1]. This is approximately 20.5% of total government spending and approximately 10% of gross domestic product [2]. Since this is expected to rise even more, strategies are needed to cut cost. One strategy is to reduce the use of health care resources (called 'medical consumption') by increasing efficiency in diagnostic testing en medical treatment.

Chest pain is one of the most common reasons for admitting patients to the cardiac emergency department (ED) [3,4] . The first challenge in these patients is to identify those patients who suffer from an acute coronary syndrome (ACS) since prognosis improves dramatically when ACS patients receive early targeted treatment[5]. The remainder, approximately 80% of chest pain patients, has no clear ACS at presentation[6]. Clinicians tend to postpone the process of decision-making. They admit these patients for clinical observation, meanwhile treating them for ACS awaiting final diagnosis. Consequently, unnecessary diagnostics and treatment are common, resulting in redundant patient burden and high cost. Accurate identification of patients with a low risk of ACS, without a need for additional work-up or hospitalization, may save use of resources and consequently, money.

The HEART score

In order to improve risk stratification of chest patients presenting in the ED and to place relative arguments for ACS into perspective, the HEART score was designed (table 1).The HEART score is assessed upon presentation in the ED. It consists of 5 components: history, electrocardiogram (ECG), age, risk factors and troponin. For each component 0, 1 or 2 points are given. This results in a final score of 0-10 points for an individual patient.

The HEART score was based on clinical experience and medical literature and designed to be as easy to use as the Apgar score for new-borns[7]. The HEART score has been validated retrospectively and prospectively in four studies A-D. The data of study A were later incorporated in study B[8,9,10,11]. The results from studies B, C and D are remarkably consistent.

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

The HEART score is strong in predicting the risk of major adverse cardiac events (MACE) within six weeks. Based on these results, patients may be classified as low risk (HEART score 0-3), intermediate risk (HEART score 4-6) and high-risk (HEART score 7-10) (Table 2).

Typically, the HEART score is assessed within one hour after the arrival of the patient in the ED. The physician uses the HEART score to take early decisions on possible additional diagnostic steps or immediate treatment. The risk of MACE in this low risk group ranges from 0.99%–2.56%, with negative predictive values ranging from 0.97–0.99 in our validation studies. Therefore, the HEART study group has suggested discharging these low risk patients without further work-up. This policy may result in reduction of health care resources and cost of health care.

Table 2. Risk of MACE and negative predictive values of the HEART score

HEART score group	**Study**	**Risk of MACE** n (%)		**NPV**[ζ] (95% Confidence Interval)
≤ 3	A	1/39	(2.56)	0.97 (0.95 – 1.00)
	B	3/303	(0.99)	0.99 (0.98 – 1.00)
	C	15/870	(1.72)	0.98 (0.98 – 0.99)
	D	20/820	(2.44)	0.98 (0.97 – 0.98)
4 -6	A	12/59	(20.3)	
	B	48/413	(11.6)	
	C	183/1101	(16.6)	
	D	215/1622	(13.3)	
≥ 7	A	16/22	(72.7)	
	B	107/164	(65.2)	
	C	209/417	(50.1)	
	D	207 /464	(44.6)	
		Total	6174[¥]	

[ζ] *Negative predictive value*
[¥] *The patients of study A are included in study B*

This study was designed to analyse and describe the medical consumption within the different risk groups, and to compare data from various hospitals. The aim was to establish understanding of the extent of resources used for the diagnosis and treatment of chest pain patients. In addition, the potential of the HEART score in reducing this medical consumption, in particular in low risk patients, was analysed.

METHODS

Patient selection

Study C was conducted in 10 hospitals in The Netherlands in 2009 [10]. Patient data for the current study were retrieved from three hospitals: Hospital I; a university hospital with 1000 hospital beds, Hospital II; a community hospital with 602 beds and Hospital III; a community hospitals with 262 beds. The university hospital was the only centre performing emergency percutaneous coronary intervention (PCI) and cardiothoracic surgery. Complete

consecutive series of cases were obtained from hospitals I and III. A selection of cases from hospital II was randomly chosen in order to obtain a sample in the same order of magnitude as in the other two participating hospitals.

Exclusion criteria

In case of incomplete data, patients were excluded from the analysis. Every patient could only be included once; recurrent ED visits were scored as medical consumption and not seen as a second index presentation.

Inclusion criteria and definitions Study C

Details of the inclusion criteria and definitions are given in a previous publication [10].

Endpoints

The primary endpoint in study C was the occurrence of a major adverse cardiac event (MACE), within six weeks of initial presentation. MACE consists of: Acute myocardial infarction (AMI), PCI, CABG, coronary angiography revealing procedurally correctable stenosis managed conservatively, and death due to any cause. More details on the definitions of MACE are given in previous publications [10].

Data selection and analysis

Data were selected using the hospital's electronic patient database. In the few cases in which the electronic system did not provide complete data, paper charts were checked. In case of a transfer of the patient to another hospital discharge data from elsewhere were requested.

Scoring of cardiology related consumption started as of the ED presentation. Routine investigations (Electrocardiography (ECG), chest X-ray and laboratory tests) done in the ED were not part of the medical consumption analysis. In case of a recurrent ED visit, all routine investigations were scored.

Hospitalization was scored by hospital bed-day, according to the hospital accounting system. Consequently, a hospital bed-day was counted if a patient was admitted for at least two hours or more and if a patient was admitted before 20h00. If patient was

admitted later than 20h00, the following day was scored as the first hospital bed-day.
In case of a temporary transfer for a coronary intervention after which the patient returned immediately to the initial hospital, a hospital bed-day was scored for both hospitals.
In one hospital, patients were often admitted to the coronary care unit (CCU) for several hours, before being transferred to the ward. Therefore, the category 'short stay CCU' was created for patients staying at the CCU for six hours or less.

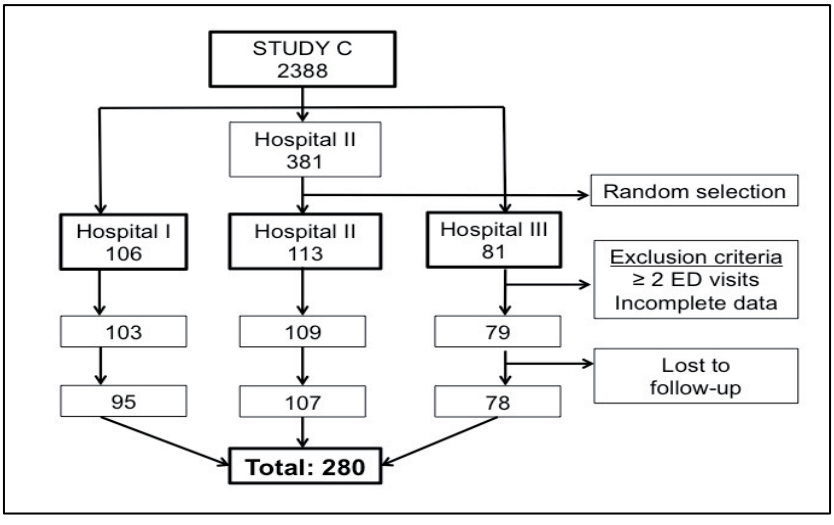
Non-conclusive cases were discussed in the adjudication committee until consensus was reached. Data analysis was performed using Microsoft Excel 2011.

RESULTS

Patients

Three hundred patients were selected from an initial cohort of 2388 patients. All patients were included between May and November 2009. Nine patients were excluded due to incomplete data and eleven were lost to follow-up due to transfer to other parts of the country, resulting in 280 patients included in this study. The patient flowchart is represented in figure 1.

Figure 1. Patient flowchart



Patient characteristics are presented in table 3. Study participants had a mean age of 60.4 +/- 15.1 years and 50.4% were male. Typically, patients had various cardiovascular risk factors for coronary artery disease and a family history of cardiovascular disease. In terms of patient characteristics, the study population was a representative sample from the complete study cohort of 2388 patients.

Table 3. Patient characteristics

n (%)	Hospital I	Hospital II	Hospital III	Total	STUDY C
Patients (n)	95	107	78	280	2388
Mean age (years, SD)	60.7 (15.4)	59,9 (16.4)	61.0 (14.4)	60.4 (15.5)	60.6 (15.4)
Male gender	54 (56,8)	48 (44.9)	39 (50,0)	141 (50.4)	1372 (57.5)
Diabetes Mellitus	23(24,2)	12 (11.2)	14 (17.9)	49 (17.5)	444 (18.6)
Smoker	34 (35.8)	41 (38.3)	30 (38.5)	105 (37.5)	779 (32.7)
Hypercholesterolemia	37 (38.9)	28 (26.2)	25 (32.1)	90 (32.1)	856 (35.8)
Hypertension	42 (44.7)	47 (43.9)	30 (38.5)	119 (42.5)	1034 (43.3)
Family History	22 (23.2)	38 (35.5)	34 (43.6)	94 (33.6)	866 (36.3)
Obesity	20 (21.1)	22 (20.6)	27 (34.6)	69 (24.6)	582 (24.4)
History of AMI	20 (21.1)	9 (8.4)	8 (10.3)	37 (13.2)	379 (15.9)
History of CABG	15 (15.8)	8 (7.5)	6 (7.7)	29 (10.4)	243 (10.2)
History of PCI	19 (20.0)	22 (20.6)	8 (10.3)	49 (17.5)	510 (21.4)
History of Stroke	3 (3.2)	2 (1.9)	6 (7.7)	11 (3.9)	112 (4.7)
History of PAD	10 (10.5)	5 (4.7)	1 (1.3)	16 (5.7)	110 (4.6)

AMI: Acute myocardial infarction, CABG: Coronary Artery Bypass Grafting, PCI: Percutaneous Coronary Intervention, PAD: Peripheral Artery Disease.

The distribution of the HEART score is presented in table 4, showing the number of patients per HEART score for every study group. Distribution of the HEART score per risk group corresponds well between this study population and the patients included in the initial cohort of 2388 patients.

Table 4. Distribution of the HEART score

HEART score	Hospital I (n,%)	Hospital II (n,%)	Hospital III (n,%)	Total (n,%)	STUDY C (n,%)
0	5 (5.3)	2 (1.9)	1 (1.3)	8 (2.9)	55 (2.3)
1	5 (5.3)	10 (9.3)	7 (9.0)	22 (7.9)	157 (6.6)
2	9 (9.5)	14 (13.1)	11 (14.1)	34 (12.1)	295 (12.4)
3	16 (16.8)	16 (15.0)	6 (7.7)	38 (13.6)	363 (15.2)
Low risk	**35 (36.8)**	**42 (39.3)**	**25 (32.1)**	**102 (36.4)**	**870 (36.4)**
4	16 (16.8)	14 (13.1)	16 (20.5)	46 (16.4)	390 (16.3)
5	13(13.7)	10 (9.3)	9 (11.5)	32 (11.4)	395 (16.5)
6	12 (12.6)	15 (14.0)	16 (20.5)	43 (15.4)	316 (13.2)
Intermediate	**41 (43.2)**	**39 (36.4)**	**41 (52.6)**	**121 (43.2)**	**1101 (46.1)**
7	9 (9.5)	13 (12.1)	3 (3.8)	25 (8.9)	204 (8.5)
8	6 (6.3)	9 (8.4)	8 (10.3)	23 (8.2)	133 (5.6)
9	2 (2.1)	4 (3.7)	0 (0.0)	6 (2.1)	58 (2.2)
10	2 (2.1)	0 (0.0)	1 (1.3)	3 (1.1)	22 (0.9)
High risk	**19 (20.0)**	**26 (24.3)**	**12 (15.4)**	**57 (20.4)**	**417 (17.5)**
Total	95	107	78	280	2388

Low risk: a HEART score of 0 to 3 points, Intermediate risk: a HEART score of 4 to 6 points, High risk: a HEART score of 7 to 10 points.

Table 5 represents the distribution of MACE in each HEART score category in the participating hospitals and the original study. MACE within six weeks did not occur in the low risk group of the sub study. Percentages within the intermediate and high-risk group differ between hospitals.

Table 5. Distribution of MACE per HEART score (number of patients)

HEART score	Hospital I (n,%)	Hospital II (n,%)	Hospital III (n,%)	Total (n,%)	STUDY C (n,%)
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.5)
Low risk	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**15 (1.7)**
4	2 (12.5)	3 (21.4)	3 (18.8)	8 (17.4)	35 (9.0)
5	1 (7.7)	2 (20.0)	0 (0.0)	3 (9.4)	54 (13.7)
6	8 (66.7)	5 (33.3)	2 (12.5)	15 (34.9)	94 (29.7)
Intermediate	**11 (26.8)**	**10 (25.6)**	**5 (12.5)**	**26 (21.5)**	**183 (16.3)**
7	3 (33.3)	6 (46.2)	0 (0.0)	9 (36.0)	90 (44.1)
8	5 (83.3)	4 (44.4)	4 (50.0)	13 (56.5)	64 (48.1)
9	2 (100.0)	3 (75.0)	-	5 (83.3)	40 (69.0)
10	1 (50.0)	-	1 (100.0)	2 (66.7)	15 (68.2)
High risk	**11 (57.9)**	**13 (50.0)**	**5 (41.7)**	**29 (50.9)**	**209 (50.1)**
Total	22 (23.2)	23 (21.5)	10 (12.8)	55 (19.6)	407 (17.0)

Tables 6 and 7 represent the medical consumption in patients with low, intermediate and high HEART scores.

Low risk patients

Exercise testing and echocardiography were the non-invasive diagnostic tests most often performed in low risk cardiology patients. A small percentage of the low risk patients had computed tomography (CT) or single photoemission computed tomography (SPECT). All CT scans were made for ruling out pulmonary embolism (PE) and/or aortic dissection. Five low risk patients (4.9%) had coronary angiography. In one of these patients significant coronary artery disease was diagnosed,

which was treated conservatively. This diagnosis was made three months after the index presentation and was therefore not scored as a MACE. Eighteen patients (17.6%) were admitted, with in a total of 28 hospital bed-days. After presentation, 9.8% of the patients returned to the ED once or more often. Of all low risk patients, 5.9% was repeatedly admitted to the hospital for various reasons and 24.9% had follow-up in the outpatient clinic (OPC).

Table 6. Non-invasive diagnostic modalities (chest X-ray, function tests, other radiological imaging) and coronary angiography per site and per risk group (percentage of patients)

	Site	Chest X ray %	Exercise %	Holter %	Echo %	CT %	SPECT %	CAG %
LOW	I	14.3	22.9	0.0	25.7	2.9	8.6	5.7
	II	2.4	33.3	9.5	7.1	4.8	7.1	4.8
	III	12.0	20.0	0.0	16.0	8.0	-	4.0
	TOTAL	**8.8**	**26.5**	**3.9**	**15.7**	**4.9**	**5.9**	**4.9**
MEDIUM	I	31.7	19.5	2.4	41.5	4.9	7.3	4.9
	II	15.4	25.6	0.0	17.9	2.6	12.8	35.9
	III	17.1	51.2	0.0	26.8	2.4	2.4	9.8
	TOTAL	**21.5**	**32.2**	**0.8**	**28.9**	**3.3**	**7.4**	**16.5**
HIGH	I	52.6	21.1	10.5	36.8	15.8	10.5	31.6
	II	42.3	23.1	3.8	50.0	3.8	7.7	61.5
	III	25.0	50.0	0.0	50.0	0.0	-	41.7
	TOTAL	**42.1**	**28.1**	**5.3**	**45.6**	**7.7**	**7.0**	**47.4**

Echocardiogram, CT: Computed tomography, SPECT: single photon emission computed tomography, CAG: Coronary angiogram.

Intermediate and high-risk patients

In these groups, percentages of patients having echocardiography, chest X-rays, CAG, invasive treatment, initial admission and follow-up (OPC) went with the increasing risk of MACE. In the intermediate group, 16.5% of the patients underwent CAG. Over 30% of the patients were hospitalized and 71.9% had follow-up in the OPC. In high-risk patients a CAG was performed in 47.7% of the patients. Over 70% of the high risk patients were hospitalized and 84.2% of the high-risk patients had follow-up in the OPC.

Table 7. Invasive treatment and admission per site and per risk group (percentage of patients)

	Site	PCI %	CABG	Ward %	CCU %	CCU short %	Re-ED %	Re-ad %	OPC %
LOW	I	0.0	0.0	8.6	17.1	-	17.1	5.7	20.0
	II	0.0	0.0	0.0	9.5	-	4.8	4.8	42.9
	III	0.0	0.0	12.0	4.0	12.0	8.0	8.0	20.0
	TOTAL	**0.0**	**0.0**	**5.9**	**10.8**	**2.9**	**9.8**	**5.9**	**29.4**
MEDIUM	I	14.6	4.9	29.3	36.6	-	17.1	22.0	70.7
	II	23.1	2.6	17.9	33.3	-	23.1	28.2	76.9
	III	4.9	2.4	58.5	26.8	36.6	17.1	12.2	68.3
	TOTAL	**14.0**	**3.3**	**35.5**	**32.2**	**12.4**	**19.0**	**20.7**	**71.9**
HIGH	I	36.8	5.3	52.6	68.4	-	5.3	15.8	68.4
	II	30.8	15.4	46.2	76.9	-	23.1	34.6	92.3
	III	33.3	16.7	91.7	75.0	8.3	0.0	25.0	91.7
	TOTAL	**33.3**	**12.3**	**57.9**	**73.7**	**1.8**	**12.3**	**26.3**	**84.2**

PCI: percutaneous coronary intervention, CABG: Coronary artery bypass grafting, CCU: Coronary care unit, CCU short stay: Coronary care unit for ≤ 6 hours, Re-ED: recurrent ED visit (≥1), Re-ad: recurrent admission (≥1), OPC: Out patient clinic.
NB: Patients are often initially admitted to the CCU and transferred to the ward afterwards. In the case of these patients, both CCU and ward are scored.

Medical consumption in low-risk patients

Additional work-up was performed in 52 out of 102 low-risk patients (51%). Twelve of these patients (23.1%) had this additional work-up for a diagnosis other than suspected ACS. These diagnoses included: six suspected pulmonary embolisms (PE), five supraventricular tachycardias and one suspected left ventricular hypertrophy. The five patients who underwent CAG were not among these twelve. The reason to perform CAG in these patients was persistent chest discomfort. One turned out to be positive for significant coronary artery disease (CAD), which was treated conservatively. The remaining four CAG's were negative for CAD.

DISCUSSION

Medical consumption

Medical consumption was analysed in 280 patients in three hospitals in the Netherlands. Patients were classified according to their risk of MACE (low, intermediate or high risk) as predicted by the HEART score.

The baseline characteristics, distribution of the HEART score and risk of MACE, indicate a proper representation of the initial cohort of 2388 patients in the main study. This is also supported by the observation that the risk of MACE is similar within the group of low risk patients in the three different hospitals. This again shows that the HEART score is applicable in different ED settings.

This study shows remarkable differences between hospitals in the percentage of patients receiving further assessment or additional treatment. In particular, these differences concern intermediate and high-risk patients. The varying occurrence of MACE and the different facilities available in these hospitals explain some of these differences. Other reasons remain to be resolved.

Low risk patients

In the low risk group (HEART score ≤ 3), 40/102 (39.2%) patients underwent additional work-up for the identification of ACS/CAD. Significant CAD was diagnosed in only one patient (2.5%). Thirty-nine patients (97.5%) underwent additional testing or received treatment, resulting no diagnosis of coronary artery disease made in any patient. This may be interpreted as a waste

of healthcare resources and (tax) money. Another objection may be that the patients have been disposed to the risks of iatrogenic damage.

Acceptable Risk

In previous studies we found a rate of false negatives in terms of prediction of MACE ranging from 0.99% – 2.56%.**Fout!Bladwijzer niet gedefinieerd.,Fout!Bladwijzer niet gedefinieerd.,Fout!Bladwijzer niet gedefinieerd.,Fout!Bladwijzer niet gedefinieerd.** Therefore, the HEART score study group has suggested a policy of early discharge of patients with HEART scores ≤ 3 without further work-up. A similar policy was suggested by Mahler et al, after analysis of 1070 chest pain patients (904 low risk, 166 high-risk) in a third referral centre in the United States[12]. This study showed an occurrence of MACE of 0.6% in low-risk patients (HEART score ≤ 3). The authors state "…using a HEART score of ≥4 to determine the need for cardiac testing would have reduced cardiac testing by 85%."

Mortality

According to The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology, "… an annual cardiovascular mortality of > 2% is deemed high risk, while an annual cardiovascular mortality of <1% is considered low risk, and 1-2% intermediate risk" [13]. In the pooled results of our three validation studies, the risk of MACE was 1.9% in patients with HEART score ≤ 3. This does not imply that these low risk patients will automatically end up with an unexpected sudden death. Most patients with a missed diagnosis of significant coronary artery disease are likely to suffer from a recurrent chest pain for which they will be re-evaluated. The only thing that really worries the clinician is sudden death in ACS shortly after discharge. In our three validation studies we identified 1993 patients (32.0%) with HEART score ≤ 3, of whom one patient died due to a possibly cardiac cause, a 90-year-old female with heart failure, atrial fibrillation and various tumors. The risk of death (unless clearly non-cardiac) in the low-risk group was 0.05%. Therefore, it is questionable whether additional diagnostic work-up makes sense in an on average 60-years old patient population that has a

documented risk of MACE of ≤ 2.5%. A prolonged stay in the cardiology clinic and additional diagnostic procedures are rather likely to increase the number of false positives (resulting in even more redundant medicine) than to reduce the number of false negatives.

Limitations

The assessor of the different elements of the HEART score (not calculating the HEART score itself) was also the treating physician. The knowledge of the HEART score may have influenced the treating physician.

This study was conducted in an observational and retrospective manner, as a sub study of a prospective study. The disadvantage of a retrospective analysis may be an interpretation bias. This effect is expected to be low in this case. Data were scored according to whether or not a test was performed, or an admission occurred, irrespective of the outcome.

The figures presented in this study are an underestimation of total medical consumption. Our study analysed in-hospital, cardiology-related medical consumption, and ignored other medical consumption. In addition, we were unaware of possible patient visits to other hospitals, if any.

CONCLUSIONS

Based on the HEART score, one third of the patients with chest pain visiting the ED may be classified as low-risk. Since the risk of MACE in these patients is ≤ 2.5%, limited medicine is indicated. In our study population, 18% of these low-risk patients were hospitalised, 26.5% had an exercise test, 15.7% an echocardiogram and 4.9% a coronary angiogram. Improved risk stratification in chest pain patients may theoretically result in a reduction of medical consumption.

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Chapter 12

The value of clinical and laboratory diagnostics for chest pain patients at the emergency department

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ABSTRACT

Background: The focus during the diagnostic process for patients with acute chest pain at the cardiac emergency department (ED) is to discriminate patients who may be safely discharged from those who are at risk for an acute coronary syndrome (ACS). In current practice, patients are assessed by means of anamnesis, ECG, age and risk factors by the physician and blood samples are taken at the same time to measure the cardiac marker troponin. In this study the predictive value of the clinical examination is compared with laboratory testing of troponin and with the HEART score.
Methods: This study included 720 chest pain patients who presented in the ED of two hospitals in the Netherlands. Clinical examination and laboratory testing were combined in the HEART score. The aria under the curve (AUC) of the clinical presentation, troponin and the HEART score for the occurrence of major adverse coronary events (MACE) within six weeks were calculated. In addition, the improvement of HEART with the second troponin measurement (HEART2) was assessed using the net reclassification improvement (NRI).
Results: Ten patients (1.4%) were lost to follow up. 145/710 patients (20.4%) were diagnosed with MACE. AUCs for the occurrence of MACE were 0.76 for the clinical evaluation, 0.72 for troponin and 0.82 for the HEART score. A second troponin measurement was available in 437 patients (62%). MACE occurred in 129/437 patients (29.5%). The assessment of a second troponin test resulted in an NRI of 8.0% in favor of HEART2.
Conclusion: The clinical data of chest patients in the ED obtained by the physician and results from laboratory testing should be used together to distinguish low- and high-risk patients. The HEART score, that combines both, should be used to discriminate patients at risk of a cardiac event from those who can be safely discharged. A second troponin measurement slightly improves the discriminative ability of the HEART-score.

INTRODUCTION

The focus during the diagnostic process for patients with acute chest pain at the cardiac emergency department (ED) is to discriminate patients who may be safely discharged from those who are at risk for an acute coronary syndrome (ACS). This diagnostic process should be performed quickly and efficiently, since the prognosis improves dramatically when ACS patients receive early treatment[1]**.** In current practice, patients are assessed by means of anamnesis, ECG, age and risk factors by the physician and blood samples are sent to the laboratory to measure the cardiac marker Troponin. The recently described HEART-score[2,3], combines these elements into a clinically useful risk score to stratify patients into low, intermediate and high risk for the occurrence of ACS. HEART is the acronym of History (anamnesis), ECG, Age, Risk factors and Troponin. The composition of the HEART score is given in table 1. Based on the HEART-score patients may be discharged, admitted for further observation with additional diagnostics or treated aggressively. In case additional diagnostics are required, cardiac markers are essential. The diagnostic procedure for chest-pain patients is pictured as a flow-chart in figure 1.

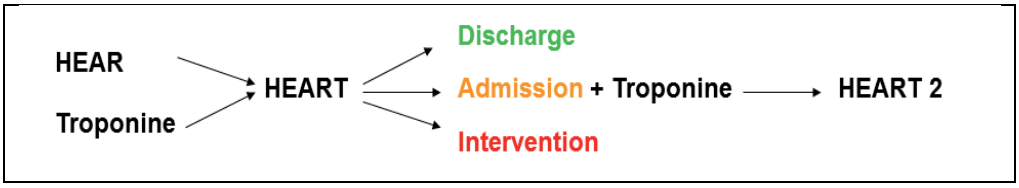
The question remains whether clinical examination performed by the physician or the measurement of troponin can each be used individually or should be used together during the diagnostic procedure of chest pain patients. In this study the predictive value of the clinical examination, which consists of the four components anamnesis, ECG, age and risk factors, on one hand is compared with laboratory testing of troponin on the other hand. Secondly, both the clinical examination and laboratory testing were compared with the HEART score (0-10).

A second question remains whether the HEART-score at presentation in the (cardiac) ED is as powerful to discriminate low- and high-risk patients as the HEART score based on the second troponin measurement (HEART2). Therefore, the clinical benefit of HEART2 was compared with HEART.

Table 1. Composition of the HEART score for chest pain patients

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Figure 1. The diagnostic procedure for chest-pain patients pictured as a flow-chart.



After presentation at the (cardiac) emergency department patients are assessed on anamnesis, ECG, age and risk factors for clinical evaluation and Troponin levels are measured. With these elements the HEART-score can be calculated and the clinical decision is made. In selective patients a second Troponin test will be performed, resulting in a HEART2 score.

METHODS

Participants

This is an observational sub study conducted at two out of ten hospitals that participated in a prospective validation study for the HEART score. Both hospitals are located in the Netherlands. One is an academic hospital with 1339 beds and one a community-based teaching hospital with 925 beds. All patients presenting in the ED with chest pain, irrespective of age, pre-hospital suspicions and previous medical treatment, were included in the study. Patients with dyspnea or palpitations as presenting symptoms were not included. If during transport to the hospital significant ST-segment-elevations on the ECG were recorded, patients were immediately taken to the nearest available coronary-intervention room in the area and therefore, are not presented in the ED. Therefore**,** patients with ST-elevation acute myocardial infarction (STEMI) at presentation were typically not included in this study. However, some exceptional patients who developed an acute myocardial infarction (AMI) during their stay in the ED were included.

In a subgroup of the patients a second troponin level was measured. Most of these patients were admitted for observation, and typically, treatment with triple anticlotting drugs (aspirin, clopidogrel and a low molecular weight heparin) was started, even in case of an unconfirmed diagnosis of ACS. In patients who were discharged immediately from the hospital after clinical assessment by the physician, second troponin levels were not taken.

The ethics committees of the participating hospitals approved the study. As this was an observational and not an intervention study, informed consent procedures were waived. However, we did inform patients about data registration and follow-up policy.

Data acquisition and management

ED residents recorded initial patient data on the admission Case Report Form (CRF), before laboratory values were known. These data consisted of separate entries for classical elements of patient history, cardiovascular risk factors, medication, physical examination and past medical history. Laboratory results, including troponin-T levels in the first hospital (reference value

<0.010 µg/L) and troponin-I levels in the second hospital (reference value <0.050 µg/L), were collected throughout the study period starting at the moment of admission and were typically repeated after six hours. A copy of the admission ECG was added to the study files. A secured web-based database was built for this study.

HEART-score criteria

The acronym HEART stands for History, ECG, Age, Risk factors and Troponin. Grading patients with the HEART-score was described in detail previously[2,3] and is represented in table 1. Briefly, the patient History was classified upon arrival of the patient by the resident in charge with regards to aspecific or suspicious elements for coronary ischemia. The ECGs, taken at the (cardiac) emergency department, were retrospectively classified according to Minnesota criteria[4] by two experienced cardiologists. In case of disagreement, a third cardiologist was consulted. We divided patients into three Age groups. The amount of classical Risk factors for coronary artery diseases was counted for each patient. The following risk factors were taken into account: treatment for diabetes mellitus, current or recent smoker (< 90 days), hypertension, hypercholesterolemia, family history of coronary artery disease, obesity (BMI > 30) or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, stroke or peripheral arterial disease) irrespective of the risk factors for coronary artery disease. Troponin T or I levels were measured according to local laboratory standards and the hospital's lower limit of normal (LLN) was used as cut-off.

Follow-up data

Follow-up data were retrieved from digital and written patient records, including discharge letters, revascularization reports and any other relevant documentation. In case follow-up data were not available from hospital records, the patient or their general practitioner was called in order obtain information on his or her condition, hospital admissions, myocardial infarction and revascularization. Patients without an event and follow-up less than 42 days were excluded from the analysis.

Endpoints

The diagnosis of acute myocardial infarction (AMI) was made according the applicable guidelines when the protocol was written, the joint ESC-ACCF-AHA-WHF task force for the redefinition of myocardial infarction[5], and consisted of a rise and/or fall of troponin values with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia. Within the diagnosis of AMI, distinction was made between either:

i. ST-elevation myocardial infarction (STEMI), defined as a syndrome consisting of a rise and fall of troponin values as described above, typical patient history and transient ST segment elevations on the consecutive 12 lead ECGs,

or:

ii. non ST-elevation myocardial infarction (NSTEMI), defined as a syndrome consisting of a rise and fall of troponin values as described above, typical patient history and persistent or transient ST-segment depression or T-wave inversion, flat T-waves, pseudo-normalization of T-waves, or no changes at presentation.

In case of rises of troponin levels without evidence of myocardial ischemia or in case of non-availability of data the case was discussed in the adjudication committee where a final diagnosis was made according to the guidelines [1,5,6].

Percutaneous coronary intervention (PCI) was defined as any therapeutic catheter intervention in the coronary arteries. Coronary artery bypass graft (CABG) surgery was defined as any cardiac surgery in which coronary arteries were operated on.

The primary endpoint in this study was the occurrence of a major adverse cardiac event (MACE), within six weeks of initial presentation. MACE consists of: AMI, PCI, CABG, coronary angiography revealing procedurally correctable stenosis managed conservatively, and death due to any cause.

Coronary angiography revealing procedurally correctable stenosis managed conservatively was defined as significant coronary stenosis thought to be the cause of the chest pain, but revascularization was withheld for reasons of co-morbidity or risk of complications.

Secondary endpoints

Secondary endpoint was the diagnosis of ACS within three months after presentation. The spectrum of ACS was described according to the definitions in the guideline for non-ST-segment elevation acute coronary syndrome[1,6] and consisted of:

i. definite ACS, defined as: STEMI or NSTEMI (as defined above), or
ii. suspected ACS, defined as: likely to be an ACS based on typical patient history consistent with unstable angina and ST-segment depression or T-wave inversion or significant stenosis at coronary angiography, but without a rise of troponin levels

Statistical analysis

For each patient the sum of the four elements for clinical assessment, the laboratory testing (TroponinT/I) and the HEART-score were calculated. Statistical analysis was performed with PASW Statistics 17.0 SPSS (IBM). For MACE and ACS the receiver-operator-characteristic curves (ROC-curve) were drawn and the corresponding area-under-the-curve (AUC) was calculated. This AUC was computed in order to give a measure of diagnostic discriminative strength, combining sensitivity and specificity, especially for non-binomial variables.

In patients with a second troponin measurement, the HEART2 score was calculated, using the second available troponin value. In order to compare the HEART and HEART2 scores the Net Reclassification Improvement (NRI) was used as described by Pencina et. al..[7] This NRI studies up- and downward movement of patients with and without an event when changes to the risk score are made, like with HEART and HEART2. In order to calculate the NRI, patients were divided into groups of low (0-3 points), intermediate (4-6 points) and high risk (7-10 points) for a cardiac event based on the HEART and HEART2 scores.

RESULTS

Study population

A total of 720 patients were included from May until December 2009 at the participating hospitals. Mean age was 62.1 +/- 15.1 year and 60.1% was male. Ten patients had a follow up

duration of less than 42 days. The mean follow-up of the remaining 710 patients was 259.7 +/- 139.9 days. The mean HEART score was 4.69 +/- 2.2. A second troponin level was available for 437 patients (62%). A comparison of the patient characteristics of the entire study group and the selection of patients with multiple troponin values is given in table 2. MACE occurred more frequently in the subpopulation of patients with second troponin measurement.

Table 2. Patient characteristics

Total Study group (N+%)	720		437	
	N	%		%
Mean age (mean+SD)	62.1	(15.1)	63.9	(14.0)
Male gender	433	60.1	276	63.2
Diabetes Mellitus	150	20.8	106	24.3
Smoker	214	29.7	131	29.6
Hypercholesterolemia	314	43.6	221	47.6
Hypertension	325	45.1	217	48.9
Family History	267	37.1	177	40.0
Obesity	208	28.9	128	28.9
History of AMI	149	20.7	102	23.0
History of CABG	94	13.1	69	15.6
History of PCI	185	25.7	124	28.0
History of Stroke	31	4.3	23	5.2
History of peripheral arterial disease	35	4.9	26	5.9
Use of Ascal	321	44.6	219	49.4
Use of Plavix	97	13.5	72	16.3
Use of Coumarine	88	12.2	61	13.8
Mean HEART score	4.69	2.2	5.46	2.2
Events/MACE	145	20.1	129	29.3
AMI	50	6.9	44	10.0
PCI	98	13.6	87	19.8
CABG	16	2.2	16	3.7
Significant stenosis	18	2.5	15	3.4
Death	4	0.6	4	0.9
ACS	163	22.9	145	33.2
Troponin level				
Follow-up period (mean+SD)	262.5	(139.3)	253.2	(144.1)

Primary end points

One fifth (145/710, 20.4%) of the patients were diagnosed with MACE within 6 weeks. In 50 (7.0 %) patients the diagnosis of AMI was made; 42/50 AMI's were diagnosed at presentation: 38 NSTEMI and 4 STEMI. With respect to therapy, 98 patients (13.8%) underwent PCI, 16 patients (2.3%) had a CABG and 18 patients (2.5%) had significant coronary artery disease for which conservative treatment was advised. Four patients (0.6%) died within 6 weeks after presentation. An acute coronary syndrome within three months occurred in 163 (22.9%) patients.

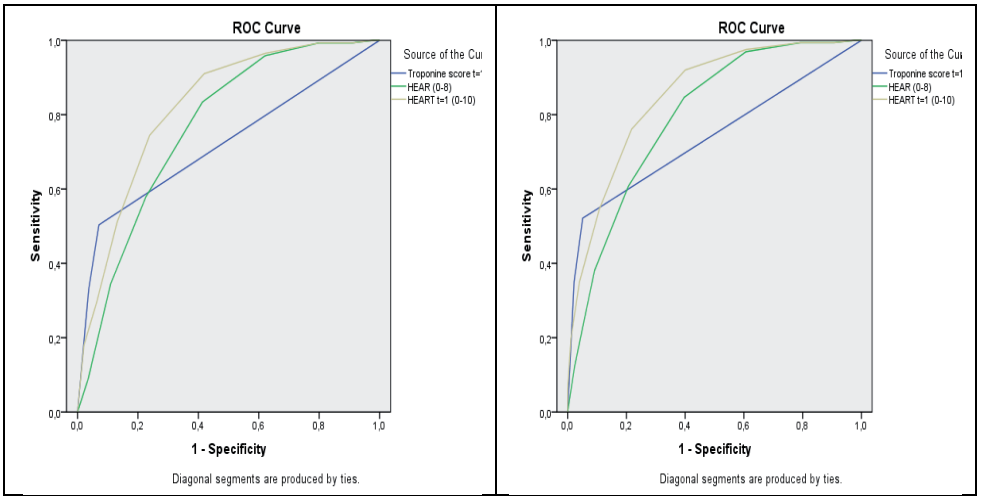
Statistical significance

The average scores for the clinical evaluation and troponin levels and the HEART-scores for patients with and without MACE and ACS are given in Table 3, together with the corresponding AUCs. The corresponding ROC-curves for the risk of MACE and ACS are presented in figure 2. The initial troponin measurement has the lowest predictive value for the occurrence of MACE. With an AUC of 0.82 for MACE and 0.85 for ACS, the HEART score has the highest predictive value as compared with the clinical evaluation or Troponin values.

Table 3. Average scores for the HEAR-,T- and HEART-scores for patients with and without a cardiac event classified under MACE and ACS.

	Without	*With*	*p-value*	*ROC*
	MACE			
N	565	145		
Troponin	0.11 +/- 0.41	0.83 +/- 0.89	<0.0001	0.719
Clinic	4.09 +/- 1.86	5.79 +/- 1.39	<0.0001	0.763
HEART	4.19 +/- 2.00	6.64 +/- 1.75	<0.0001	0.820
	ACS			
N	547	163		
Troponin	0.07 +/- 0.33	0.87 +/- 0.90	<0.0001	0.738
Clinic	4.00 +/- 1.86	5.91 +/- 1.36	<0.0001	0.793
HEART	4.06 +/- 1.90	6.80 +/- 1.76	<0.0001	0.850

Figure 2. ROC-curves for HEAR-, T- and HEART-scores for (a) MACE within 6 weeks and (b) ACS within 3 months (n=720).



Subpopulation

For 273 patients only a first troponin value was known. The remaining 437 patients were referred from the ED to the cardiology ward or the intervention room for further evaluation. Mean HEART score in the latter group was 5.31 +/- 2.1. MACE within six weeks occurred in 129 patients (29.5%): 44 AMI (10.1%), 87 PCI (19.9%), 16 CABG (3.7%), 15 significant stenosis with conservative treatment (3.4%) and four patients died (0.9%).

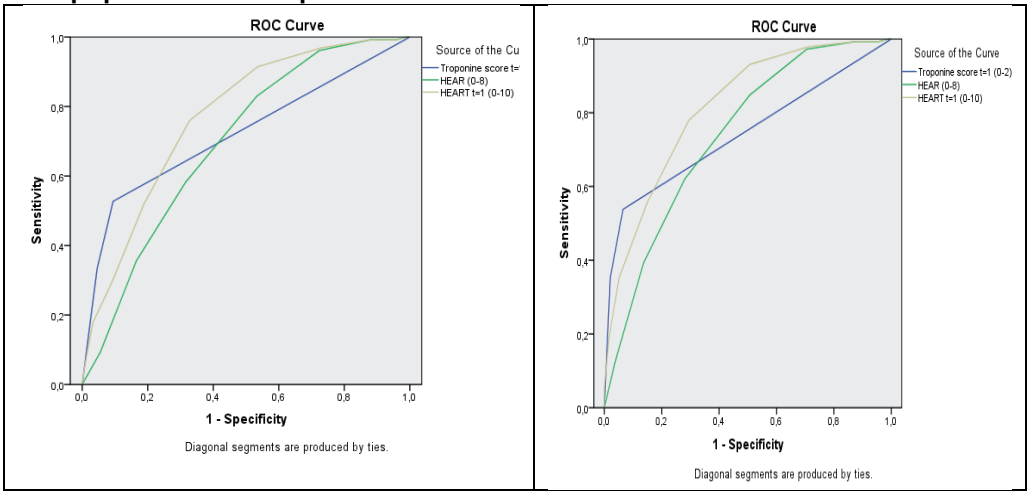
Value of second troponin measurement

The average scores for the clinical evaluation, the first and second troponin levels and the HEART and HEART 2 scores for patients with and without MACE and ACS are given in Table 4, together with the corresponding AUCs. Figure 3 presents the ROC curve for the clinical evaluation, first and second troponin value (T1 and T2) and the HEART and HEART 2 scores within the subpopulation with a second troponin measurement. The AUCs for this subpopulation are lower than for the entire study population. However the diagnostic value of the second troponin measurement increases compared to the first troponin measurement.

Table 4. Average scores for the HEAR-, T-, HEART-, T2 and HEART2-scores for patients with and without a cardiac event classified under MACE and ACS.

	Without	*With*	*p-value*	*ROC*
	MACE			
N	308	129		
Troponin	0.14 +/- 0.46	0.86 +/- 0.89	<0.0001	0.720
Clinic	4.62 +/- 1.80	5.81 +/- 1.36	<0.0001	0.694
HEART	4.75 +/- 1.95	6.67 +/- 1.73	<0.0001	0.769
Troponin 2	0.19 +/- 0.54	1.20 +/- 0.91	<0.0001	0.783
HEART2	4.81 +/- 2.02	7.01 +/- 1.77	<0.0001	0.792
	ACS			
N	547	163		
Troponin	0.09 +/- 0.35	0.89 +/- 0.90	<0.0001	0.742
Clinic	4.49 +/- 1.74	5.94 +/- 1.36	<0.0001	0.739
HEART	4.56 +/- 1.81	6.83 +/- 1.71	<0.0001	0.815
Troponin 2	0.13 +/- 0.47	1.19 +/- 0.91	<0.0001	0.798
HEART2	4.62 +/- 1.88	7.14 +/- 1.75	<0.0001	0.831

Figure 3. ROC-curves for HEAR-, T-, HEART-, T2- and HEART2-scores for (a) MACE within 6 weeks and (b) ACS within 3 months, for the subpopulation of 437 patients.



Clinical usefulness

Table 5 shows the distribution of the patients in low-, intermediate- and high-risk groups based on HEART and HEART 2 scores. In the low-risk group 4/87 (4.6%) patients had an event. None of these patients shifted to the intermediate group with the

results of the second troponin test. One patient with a low HEART score without an event shifted to the intermediate group with HEART2.

In the intermediate-risk group 46/213 (21.6%) patients had an event. Twelve of these patients shifted to the high risk group with the results of the second troponin test. Three patients with a low HEART score without an event shifted to the high risk group with HEART2. None of the intermediate patients shifted to a lower risk group after the second troponin assessment.
In the high-risk group 67/125 (53.6%) patients had an event. None of these patients shifted to the intermediate group with the results of the second troponin test.

Table 5a and 5b. Reclassification of patients using original HEART and the HEART2 score after measurement of second troponin. Patients are classified into low, intermediate and high risk for MACE (a) and ACS (b).

Table 5a

HEART	HEART 2		
	0 - 3	4 - 6	7-10
Patients without MACE(n=308)			
0 - 3	82	**1**	0
4 - 6	0	164	**3**
7 - 10	0	0	58
Patients with MACE (n=129)			
0 - 3	4	0	0
4 - 6	0	46	**12**
7 - 10	0	0	67

Table 5b

HEART	HEART 2		
	0 - 3	4 - 6	7-10
Patients without ACS(n=292)			
0 - 3	83	**1**	0
4 - 6	0	160	**4**
7 - 10	0	0	44
Patients with ACS (n=145)			
0 - 3	3	0	0
4 - 6	0	50	**11**
7 - 10	0	0	81

The clinical improvement of the HEART score with a second troponin was assessed using the NRI. The second troponin value resulted in better classification for 12 patients with MACE who shifted from the intermediate to high-risk category. On the other hand, four patients without MACE were incorrectly identified as intermediate (1) or high (3) risk after the second troponin measurement. The NRI for patients with MACE is 8.0% in favor of HEART2.

For patients with ACS, HEART 2 resulted in a better classification for 11 patients who shifted from intermediate to high-risk category. However, five patients without an ACS were incorrectly identified as intermediate (1) or high (4) risk after the second troponin measurement. The NRI for patients with ACS is 5.9% in favor of HEART2.

DISCUSSION

In current practice, patients with chest pain in the ED are stratified into low-, moderate- and high-risk groups based on data obtained from anamnesis, ECG, age, risk factors and measurement of cardiac markers. Some literature suggest that a negative troponin test implies a very low risk for cardiac events[8], while others report that low risk patients with a troponin measurement smaller than the reference value at presentation still represent a risk of AMI/unstable angina (UA) of 1.8%[9]. Furthermore, it is suggested that not the clinical presentation, but the level of troponin is the best guide to manage patients suspected for an ACS[5] and that the use of high sensitive troponin facilitates early diagnosis of acute myocardial infarction (AMI)[10,11].

In this study the predictive values for the occurrence of MACE and ACS of the initial clinical assessment of the patient by the physician, laboratory testing of the cardiac marker troponin and the HEART score were investigated. With a AUC of 0.820 for MACE and 0.850 for ACS the HEART score upon arrival of the patient carries the highest diagnostic accuracy of all three approaches. This corresponds well with previous studies that proved the HEART score to be an excellent discriminator of low, intermediate and high risk patients[2,3]. The ROC-curves for the troponin measurement, or T-score, are lower than compared with literature[12,13]. However, the troponin values in literature were

typically measured in populations with a high incidence of AMI, (up to 23%). In this study all comers with chest pain were included.

In current practice, many patients are admitted for further observation, typically to observe possible changes in ECG and rises of cardiac markers. Some suggest that it is mandatory to observe all patients until troponin is “representative”. In this study the additional effect of a second troponin test was evaluated in the diagnostic process of chest pain patients. HEART2 reaches a higher AUC than the initial HEART score in this subpopulation and is therefore a better indicator of a patients risk in a selected group as many low-risk patients have been excluded.

The fact that the AUCs in this subpopulation are slightly lower than in the initial population can be explained by the fact that many non-diseased patients, with a low risk based on clinical assessment and a negative troponin test, and consequently low HEART score, were discharged after first evaluation by de clinician. These patients usually account for a very high negative predictive value, with corresponding high AUC.

The clinical significance of an adjustment to a model may be expressed by the net reclassification improvement, as described by Pencina et al..[11] When using HEART2 instead of HEART, twelve patients with MACE or eleven patients with an ACS would be reclassified as high-risk instead of intermediate risk. These patients would benefit from aggressive treatment, which would be started with the outcome of the HEART2-score. No patients would be reclassified lower than originally with HEART. This demonstrates that a so-called ‘representative troponin’, measured approximately six hours after the chest pain episode, improves the relevance of the HEART score for selected patients’ treatment. However, in patients without MACE or ACS, slight rises of troponin levels also account for five patients without MACE and six patients without ACS who were falsely classified as intermediate or high risk. The admission of these non-diseased patients would cause unnecessary occupation of hospital beds and associated medical costs. With the population’s increasing age and advancing medical techniques, healthcare cost is a critical issue in many countries. Secondly, when these patients are treated as diseased or ACS patients awaiting the final

diagnosis during admission, the possible adverse events resulting from medication and diagnostic procedures are another critical issue.

Limitations

Since this was an observational study, second troponin values were not available in one-third of the study population. The remainder consists of mainly low-risk patients who were discharged after initial assessment. It should be noted that only the troponin was reevaluated, whilst the clinical assessment was not repeated.

CONCLUSION

In order to discriminate patients who present with chest pain in the ED into high- and low-risk for a cardiac event the clinical evaluation process should be performed quickly and efficiently. In this study we have demonstrated that clinical data (anamnesis, ECG, age and risk factors) obtained by the physician and results from laboratory testing (troponin) should be used together. The HEART score, which combines clinical data and laboratory testing, may be used to properly discriminate patients at risk of a cardiac event from patients who can be safely discharged. A second troponin measurement improves the HEART-score to discriminate patients with and without risk of a cardiac event.

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Part one
Introduction

Part Two
The HEART score validation studies

Part Three
The HEART score sub studies

Part Four
Appendix

Part Five
Summary and acknowledgements

Chapter 13

Progress report of the HEART validation program

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2 UMC Utrecht, department of Cardiology

The HEART score is designed specifically for the early risk stratification of patients presenting with chest discomfort to the Emergency Department (ED). It categorises patients using five elements: History, ECG, Age, Risk factors and Troponin. Each of these may be scored with 0, 1 or 2 points. These five elements compose the acronym of the HEART score. The composition of the score is given in table1.

Utilization of the HEART score provides excellent determination of risk for 6-week major adverse cardiac events (MACE). The HEART score is both strong in identifying a large proportion of low-risk patients, who are potential candidates for early discharge without additional testing, and high-risk patients who are candidates for early invasive strategies.

History	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-depression	2	
	Non specific repolarisation disturbance	1	
	Normal	0	
Age	≥ 65 year	2	
	45 – 65 year	1	
	≤ 45 year	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Development of the research program

Dr Six composed this risk score spontaneously in 2006 when teaching medical students at Atrium Ziekenhuis Heerlen (NL) about multi factorial considerations when making a clinical decision. The composition was based on clinical experience and knowledge of relevant medical literature. The approach was occasionally applied in individual patients and seemed to work out properly.

Drs Backus & Six composed the acronym on 31 December 2006. In the same meeting they decided to start a scientific validation program. The first study, study A, was in chest pain patients who had visited the ED of Hofpoort Ziekenhuis Woerden, a 256-bed community based hospital in The Netherlands. In order to have 1-year follow up data immediately available for all patients, the inclusion period was arbitrarily chosen to be the first quarter 2006. The first scoring card was designed on March 21, 2007 and retrospective data collection on chest pain patients started one week later. Collaboration with Dr Kelder was sought for the statistical analysis. A first draft of the manuscript (study A) was written in August 2007, actually published one year later.

A logical next step was to conduct the same study in a multi centre setting, study B. This retrospective, multi centre evaluation was designed in summer 2007. In order to include the data from study A, the same time window of inclusion was chosen. Data collection at Utrecht, Delft and Amersfoort was performed during the year 2008. Prof Pieter Doevendans from the UMCU was prepared to supervise the program and gave support by the appointment of two medical students from his department for the conduct of the study. A first abstract was written in February 2009. The full article was published in 2010.

The scientific program, as written down in October 2008, is given in table 2.

Program rationale	The purpose of this program is to validate the HEART risk score for chest pain patients and to investigate the feasibility in daily practice.
Primary program objectives	1. To validate the HEART score in characterizing patients into low, intermediate and high risk patients 2. To compare the HEART score with exercise-ECG, coronary angiograph, multi slice CT, cardiac MRI and SPECT 3. To compare the HEART score with other chest pain risk scores, i.e. TIMI and GRACE. 4. To assess the feasibility of the (modified) HEART score in an out-of-hospital setting
Secondary program objectives	1. To optimize the elements of the HEART score 2. To assess the inter observer variability 3. To assess the accuracy of the HEART score in various patient groups such as elderly, diabetics and men/women
Patient population	Patients with chest pain, admitted to the cardiology emergency room.
Studies	One retrospective single centre study One retrospective multi centre study with five sub studies One retrospective study in GP-population (FAME) One retrospective study comparing the HEART score with multi slice CT (Groningen) One prospective multi centre study with six sub studies
Number of hospitals	10-15
Planned start and end	January 2006 – March 2011

The first preparations for the prospective study C took place in summer 2008. Ten sites were selected for participation. Dr Bosschaert built the data base.

The patient inclusion period lasted from October 2008 to November 2009, during various time intervals at the participating sites. A total of 2440 patients were included. The study analysis was completed in early 2011. The manuscript submissions started in April 2011. Various abstracts were accepted for national and international scientific meetings (listed below).

Lancet published a prospective observational study in chest pain patients in the Asia-Pacific region (the ASPECT study)

in March 2011. This study did not use the HEART score for risk stratification. A published letter to the editor of the HEART investigators on the matter resulted in an external validation of the HEART score in almost 3000 patients in 9 countries in the Asia-Pacific region (Study D). Analysis was done in autumn 2011. Manuscript is in the stage of finalization and will be submitted by the end of the year 2011.

Studies B, C and D yielded remarkably similar results, both in terms of baseline characteristics and risk of MACE in various HEART strata. A pooled results analysis is published in this thesis.

The development of the implementation study E was started in summer 2010, in co-operation with Prof Arno Hoes from the Julius Centre Utrecht. A first draft protocol was written and an application for a grant from ZonMW was made in September 2010. ZonMW allocated a major grant in November 2011. This study concerns the cost-effectiveness of implementation of the HEART score, using a stepped wedge design. 6000 patients will participate. Investigator recruitment (n=10) and ethics committee submissions are due in February 2011. Patient recruitment is planned to start in June 2012. End of project is foreseen in 2015.

Scientific validation

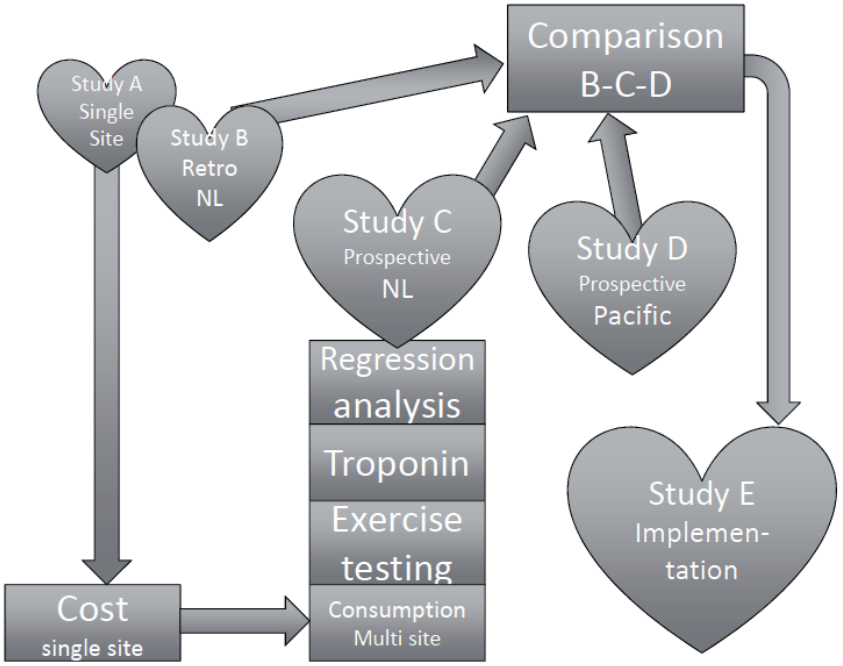
The scientific validation program of the HEART score is given in table 3.

		Period of recruitment	Number of patients	Participating hospitals	Publication #
1	Study A	1 q 2006	122	1	1
2	Study B	1 q 2006	930	4	2
3	Study C	Oct 2008- Nov 2009	2440	10	Submitted 5
4	Study D	Nov 2007- December 2010	2906	14	Submitted 8
5	Study E	FPI September 2012	6000	10	

In addition to the five general validation studies, various sub studies were conducted or are in progress. The status of the sub studies is given in table 4.

		Patient population	**Sub investigator**	**Publication #**
5	Literature comparison of risk scores	n.a.	n.a.	**Published 3**
6	Analysis of medical consumption	Study A	Ideles Kaandorp	**Submitted 7**
7	Analysis of medical consumption	Study C subset	Annelieke Kingma	Draft
8	Regression analysis	Study C	Yvonne Vergouwe	**Submitted 6**
9	Value of exercise testing	Study C	Judith Poldervaart	Draft 9
10	Inter observer variability	Study B	Thomas Mast	Analysis ongoing
11	Letter to the editor on the ASPECT study	n.a.	n.a.	**Published 4**
13	Gender differences in presentation and patient history	Study C	Manon van der Meer	Analysis ongoing
14	Sub-analysis on Hindustan patients	Study C	Rolf Veldkamp	Analysis ongoing
15	Value of additional troponin testing	Study C	LaurensJan Jellema	Draft

The relationship between the validation studies and the sub studies is given in figure 1.



Full article publications:

1. Six AJ, Backus BE and JC Kelder. *Chest pain in the emergency room: value of the HEART score.* Neth Heart J 2008;16:191-6
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3. BE Backus, AJ Six, JH Kelder, B Gibler, F Moll, PA Doevendans. *Risk Scores for Patients with Chest Pain: Evaluation in the Emergency Department.* Current Cardiology Reviews, 2011, Volume 7(1), page 2-8
4. Six AJ, Backus BE, PAFM Doevendans. *Rapid diagnostic protocol for patients with chest pain.* Lancet 2011; 378:398 (letter to the editor).

Submitted for publication

5. BE Backus, AJ Six, JC Kelder, MAR Bosschaert, EG Mast, A Mosterd, RF Veldkamp, AJ Wardeh, R Tio, R Braam, SHJ

Monnink, R van Tooren, TP Mast, F van den Akker, MJM Cramer, AW Hoes, PA Doevendans. *A simple score for the assessment of chest pain patients at the emergency room: a prospective validation study of the HEART score.* (Submitted for publication)

6. BE Backus, AJ Six, PA Doevendans, JC Kelder, EW Steyerberg, Y Vergouwe. *Prognostic factors in chest pain patients: a quantitative analysis of the HEART score*. (Submitted for publication)
7. AJ Six, BE Backus, AEC Kingma, SE Kaandorp. *Consumption of diagnostic procedures and other cardiology care in chest pain patients after presentation at the emergency department.* (Submitted for publication)
8. A Jacob Six Louise Cullen, Barbra E Backus, Jaimi Greenslade, William Parsonage, Sally Aldous, Pieter A Doevendans, Martin Than. *The HEART score for the assessment of patients with chest pain in the Emergency Department: - A multi-national validation study.* (Submitted for publication)

Manuscripts in preparation

9. A Jacob Six, Louise Cullen, Barbra E Backus, Jaimi Greenslade, Martin Than, Pieter A Doevendans. *Occurrence of MACE and death in three validation studies for the HEART score for chest pain patients at the Emergency Department*
10. LC Jellema, BE Backus, AJ Six, R Braam, B Groenemeijer, H van der Zaag, R Tio, JDE van Suijlen. *The value of clinical and laboratory diagnostics for chest pain patients at the emergency department*
11. BE Backus , AJ Six, J Poldervaart, MJM Cramer, RF Veldkamp, EG Mast, EM Buys, WJ Tietge, BE Groenemeijer, L Cozijnsen, AJ Wardeh, PA Doevendans. *Is the exercise test valuable for risk evaluation after presentation for chest pain at the emergency department?*
12. AEC Kingma, AJ Six, BE Backus, MJM Cramer, GA de Wit, A Mosterd, PJ Senden, TP Mast, PA Doevendans. *Medical consumption in chest pain patients after presentation in the emergency room*

Major lectures given on the HEART score are given in table V

Date	Location	Audience	Abstract reference
April 2009	Amsterdam	Nederlandse Vereniging voor Cardiologie	BE Backus, AJ Six, JC Kelder, TP Mast, F van den Akker, PA Doevendans. The HEART score for chest pain patients at the emergency room. Neth Heart J 2009;17
August 2009	Barcelona	European Society of Cardiology	B.E. Backus, A.J. Six, J.C. Kelder, T.P. Mast, F. Van Den Akker, P.A. Doevendans. The HEART score for chest pain patients at the emergency room. Eur Heart J 2009;30 (suppl 1); page 312 (abstract 1956)
October 2009	Amsterdam	Nederlandse Vereniging voor Cardiologie	BE Backus, AJ Six, JC Kelder, TP Mast, F van den Akker, HWL de Beaufort, EG Mast, PA Doevendans. Comparison of the HEART, TIMI and GRACE risk scores for chest pain patients at the emergency room. Neth Heart J 2009;17
March 2010	Ede	Nederlandse Vereniging voor Spoedeisende Hulp Verpleegkunde	
March 2010	Atlanta	American College of Cardiology	Barbra E. Backus, A. J. Six, J. C. Kelder, T. P. Mast, F. vanden Akker, H. W. de Beaufort, E. G. Mast, P. A. Doevendans. Comparison of the HEART, TIMI and GRACE scores for chest pain patients at the emergency room. JACC 2010;55 (10A): Abstract 1156-282 (poster)
August 2010	Stockholm	European Society of Cardiology	B.E. Backus, A.J. Six, J.H. Kelder, A. Mosterd, E.G. Mast,R. Braam, R. Tio, R. Veldkamp , P.A. Doevendans. Comparison of the HEART, TIMI and GRACE risk scores for chest pain patients at the emergency room. Eur Heart J 2010;31 (suppl 1); page 482 (abstract 2957)
October 2010	Copenhagen	Acute Cardiac Care [(b)]	
November 2010	Amersfoort	Local [(c)]	
March 2011	Reehorst Ede	Nederlandse Hartfunctie Vereniging	Six AJ. De HEART-score voor patiënten met pijn op de borst op de Eerste Harthulp en de hartfunctieafdeling.

June 2011	Egmond aan Zee	Nederlandse Vereniging voor Spoedeisende Hulp-Artsen [(d)]	
August, 2011	Paris	European Society of Cardiology	Backus BE, Six AJ, Kelder JC, Mosterd A, Mast EG, Groenemijer B, et al. A prospective validation of the heart score for chest pain patients at the ER. Eur Heart J 2011;32 (suppl 1), 952, abstract 5220
October 2011	Arnhem	Nederlandse Vereniging voor Cardiologie	B.E. Backus, A.J. Six, J.H. Kelder, E.G. Mast, A. Mosterd, R.F. Veldkamp, A. Wardeh, R. Tio, R. Braam, P.A. Doevendans. A prospective validation of the HEART score for chest pain patients at the emergency room. Neth Heart J 2011; 19

Awards:

a) *NVVC 2009: Best oral presentation*
b) *ACC 2010: Young Investigators Award*
c) *Amersfoort 2010: Wetenschap stimuleringsprijs*
d) *Egmond 2011: Best oral presentation*

In addition, lectures have been given at local health care conventions (table 6):

Date	Location	Audience	Lecturer
November, 2007	Hofpoort Ziekenhuis Woerden	Regionale refereeravond	Six
February, 2009	Apeldoorn	All cardiology staff	Backus
February, 2009	Wittenburg, Den Haag	All cardiology staff	Backus&Six
May, 2010	Kattenburg, Amsterdam	Army physicians	Six
June , 2011	Hofpoort Woerden	GPs & Em. phys.	Six
March, 2011	Diakonessenhuis Utrecht	Emergency Physician	Backus
May, 2011	Gelderse Vallei, Ede	All cardiology staff	Backus
May, 2011	Deventer ziekenhuis	All cardiology staff	Backus
May, 2011	Cremona, Italy	24 Dutch cardiologists	Six
June, 2011	Ziekenhuis Doetinchem	All cardiology staff	Backus
June, 2011	Ziekenhuis Veghel+Uden	All cardiology staff	Backus
July, 2011	JBZ, Den Bosch	All cardiology staff	Backus
August 2011	Erasmus Rotterdam	Emergency Physicians	Backus
November, 2011	TerGooi Hilversum	All cardiology staff	Backus
January, 2012	Wittenburg, Den Haag	All cardiology staff	Backus&Six

Investigators meetings for the HEART program (table 7)

Date	Site	
November 30, 2008	Sterrenburg, Utrecht	
March 19, 2009	Karel V, Utrecht	
November 25, 2009	Oudaen, Utrecht	
July 7, 2011	Adjudication meeting exercise tests	Adjudication Committee

Financial issues

- Stichting Concordia Trajectina supports the HEART study program with a fee for a one-year employment of Dr Backus at the UMCU. Stichting Concordia Trajectina receives unrestricted grants for this purpose from private parties, including Stichting Swaenenborgh, and from Medtronic.
- Astellas has supported the program with cost of printing a scoring pocket card and facilitated investigators meetings
- Novartis has supported the program with cost of printing a scoring pocket card and facilitated investigators meetings
- A major free from ZonMW for an implementation study in 6600 patients in 10 hospitals has been granted. The budget includes 3 years full time work for an investigator-in-training, part time assignment of Drs Backus and Six, statistical and methodological support etc.

Miscellaneous other issues

- *A web site www.heartscore.nl is active. Information can be found on the progress of the program and various publications are incorporated as PDF files.*
- *Monthly reports of visitors of the site is generated by means of Google Analytics . Increasing numbers of visitors are noticed from all countries of the world.*
- *In cooperation with Qx Calculate an APP for various smart phones is in the process of development.*

Chapter 14

Rapid diagnostic protocol for patients with chest pain

A.J. Six[1], B.E. Backus[2], P.A. Doevendans[2]

1 Hofpoort hospital, Woerden, The Netherlnads
2 University Medical Center, Utrecht, The Netherlands

The Lancet;378:398

Martin Than and colleagues[1] investigated a new accelerated diagnostic protocol for patients with chest pain, based on the thrombolysis in myocardial infarction (TIMI) risk score. The TIMI score was designed about 15 years ago to identify patients with high-risk acute coronary syndrome at the coronary-care unit who benefit most from aggressive anticlotting agents[2]. It consists of seven binary choices. From Than and colleagues' study it seems that this score can also be applied in the much broader chest pain population in the emergency room for recognising very low-risk patients. However, the TIMI score identifies a minority of about 10% of patients at both ends of the risk range, thus leaving 80% of the patients in the intermediate-risk category, where medical policy remains unclear. This score thus seems to leave room for improvement.

We designed the HEART score for patients with chest pain in the emergency room with only five components: history, ECG, age, risk factors, and troponin[3]. Unlike the TIMI score, history is included as well since the pattern of the chest pain is a leading symptom in this category of patients. Each of the components can be assigned 0, 1, or 2 points. In a retrospective multicentre validation study, 303 (34%) of 880 patients had HEART scores of 0-3, and the 6-week incidence of major adverse cardiac events in these patients was just 1%. In the 164 (19%) of patients with scores of 7-10, the risk of major adverse cardiac events was 65%.

Consequently, our score gives direction in clinical decision making in most patients. We expect to confirm these retrospective findings with a prospective study in 2440 patients, which is about to be completed.

We declare that we have no conflicts of interest.

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2. Antman EM, Cohen Mk, Bernink PJLM, et al. The TIMI risk score for unstable angina/non-ST elevation MI. JAMA 2000; 284:835-842.
3. Backus BE, Six AJ, Kelder JC, et al. Chest pain in the emergency room: a multicenter validation of the HEART score. Crit Pathways Cardiol 2010; 9: 164-169.

Chapter 15

More cost-effective management of chest pain patients presenting in the emergency room: application of a validated rule

B.E. Backus[1], A.J. Six[2], J.C. Kelder[3], H. Koffijberg[4], K.G. Moons[4], A. Mosterd[5], P.A. Doevendans[1], A.W. Hoes[4].

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2 Hofpoort hospital Woerden, department of Cardiology
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4 Julius Center Utrecht
5 Meander medical center, Amersfoort

Summary of application of ZonMW research grant

Summary of the implementation study

Objective: To quantify the impact of the use of the HEART risk score on patient outcome (major adverse cardiac events (MACE) and quality of life) and on costs in patients with chest pain presenting at the emergency room (ER).

Study design: Prospective stepped wedge trial including 6600 patients in ten Dutch hospitals.

Study population: 6600 unselected chest pain patients at the ER in ten hospitals in the Netherlands.

Intervention: During 11 months, patients presenting with chest pain to the ER of participating hospitals will be included in the study. First, all hospitals will apply 'usual care' to all patients, i.e. assessment without application of the HEART score. Then, during a 10 month period, each month 1 randomly allocated hospital will sequentially start to apply the HEART score (previously developed and validated by our group) in all chest pain patients (intervention period); during this intervention period patients with a HEART score 0-3 will not be admitted to the hospital (in accordance with the results of our validation studies), and patients with a HEART score above 3 will be treated according to current guidelines.

Outcome measures: All patients will be followed for three months to assess the study outcome parameters. Primary outcome: occurrence of MACE (i.e. acute myocardial infarction (AMI), Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG) or death) within 6 weeks after presentation (non-inferiority approach). Secondary outcomes: 3 months incidence of MACE, quality of life and cost-effectiveness of the intervention compared with usual care.

Economic evaluation: In a random subgroup of patients (n = 500 in the intervention and control periods, n = 1000 in total) actual direct medical costs are obtained. Also, actual indirect costs related to productivity loss are obtained, using the SF-HLQ

questionnaire. Patients' quality of life is measured, using the SF-36 and EQ-5D questionnaires, at baseline, at 2 weeks and at 3 months. A cost-effectiveness analysis is performed based on differences in cost estimates and quality of life estimates. Bootstrapping is applied to assess cost-effectiveness for a 3 month time horizon whereas a Markov decision-analytic model is applied to assess cost-effectiveness for a life-time horizon.

Samenvatting van het implementatieonderzoek

Doel: Het in kaart brengen van de invloed van het gebruik van de HEART risico score op de uitkomst (major adverse cardiac events (MACE) en kwaliteit van leven) en op de kosten bij patiënten met pijn op de borst op de spoedeisende hulp (SEH).

Studiedesign: Een prospectieve steppedwedge studie bij 6600 patiënten in tien Nederlandse ziekenhuizen.

Studiepopulatie: 6600 ongeselecteerde patiënten met pijn op de borst op de SEH in tien Nederlandse ziekenhuizen.

Interventie: Gedurende 11 maanden zullen patiënten die zich presenteren met pijn op de borst op de SEH van de deelnemende ziekenhuizen geïncludeerd worden in de studie. Eerst zullen alle ziekenhuizen bij alle patiënten gedurende 1 maand de standaard behandeling toepassen; dat wil zeggen zonder gebruik van de HEART score. Vervolgens zal gedurende 10 maanden, elke maand, 1 (at random toegewezen) ziekenhuis starten met het toepassen van de HEART score (voorheen ontwikkeld en gevalideerd door onze onderzoeksgroep) bij alle patiënten met pijn op de borst (interventieperiode); gedurende de interventieperiode worden patiënten met een score van 0-3 niet opgenomen in het ziekenhuis (conform de uitkomsten van onze validatie studies) en patiënten met een HEART score boven de 3 worden behandeld overeenkomstig de huidigerichtlijnen.

Eindpunten: Alle patiënten worden gevolgd gedurende een periode van drie maanden om het optreden van eindpunten temeten. Primaire eindpunten: De incidentie van Acuut Myocardinfarct (AMI), Percutane Coronaire Interventie (PCI), CoronaryArtery Bypass Grafting (CABG) en dood, samen MACE genoemd (Major Adverse Cardiac Events) binnen 6 weken na presentatie. Secundaire uitkomstmaten: de incidentie van MACE binnen 3 maanden, kwaliteit van leven en kosten-effectiviteit van de interventie vergeleken met de standaard behandeling.

Economische evaluatie: In een subgroep van patiënten (n=500 in de interventie- en de controle (‘usual care’) periode, n=1000 in totaal) worden daadwerkelijke directe medische kosten verzameld. Ook de daadwerkelijke indirecte kosten gerelateerd aan productieverliezen worden verzameld, met de SF-HLQ (Werk en Ziekte) vragenlijst. Gezondheidsgerelateerde kwaliteit van leven wordt gemeten met de SF-36 en EQ-5D vragenlijsten, en gemeten bij de start van de studie, op 2 weken en 3 maanden. Een kosten-effectiviteitsanalyse wordt uitgevoerd uitgaande van verschillen in geschatte kosten en kwaliteit van leven schattingen. Bootstrap methoden worden gebruikt om de kosteneffectiviteit te schatten voor een tijdshorizon van 3 maanden; een Markov besliskundig model wordt gebruikt om kosteneffectiviteit te schatten voor een levenslange tijdshorizon.

Part one
Introduction

Part Two
The HEART score validation studies

Part Three
The HEART score sub studies

Part Four
Appendix

Part Five
Summary and acknowledgements

Summary

Risk stratification in chest pain patients in the emergency department (ED) is hampered by poor diagnostic power of individual elements of clinical presentation. International guidelines of joined cardiovascular societies suggest the use of a risk score to place relative arguments into perspective and to identify carefully low or high-risk patients of a cardiovascular event. The HEART score was developed specifically for chest pain patients in the ED and follows clinical reasoning closely.

The predictive value of the HEART score for the occurrence of major cardiovascular events (MACE) in chest pain patients in the ED has been determined in a series of four scientific investigations. Data of all 6226 patients in these studies have been combined in one data set for sub group analyses. The HEART score appears a strong predictor of event free survival on one hand and potentially life threatening cardiac events on the other hand. The HEART score helps in making accurate decisions in the ED without the use of X-rays or invasive procedures. Within one hour from presentation, it identifies both (i) a large proportion of low-risk patients, with a risk of MACE of only 1.9%, and (ii) high-risk patients, with a risk of MACE of about 50%. In case of intermediate values, the HEART score is less helpful. The HEART score is an easy, quick, and reliable predictor of outcome in chest pain patients, and may be used for triage.

Older risk scores, such as PURSUIT, TIMI, GRACE and FRISC, are based on large databases of patients with proven acute coronary syndrome (ACS). These were developed after identification of independent risk factors for the primary endpoint, typically death and/or myocardial infarction (MI). Consequently, these risk scores are strong in identifying patients at the highest risk of an adverse event. Statistically, these scores have a firm basis. However, the selection of parameters and the variance in weight of the elements make these less applicable in the bedside setting. Secondly, these sores seem to ignore the vast majority of low risk patients who represent over one third of the chest pain patients in the emergency department. The HEART score is

superior compared to TIMI ad GRACE. Low-risk as well as high-risk patients in the ED are better identified by means of the HEART score, resulting in a higher diagnostic performance.

We investigated whether the diagnostic performance of the HEART score could be improved after redesigning based on multivariable regression analysis. We showed that the arbitrarily chosen weights of the five elements of the HEART score leave room for improvement by means of adapting the score based on statistical analysis. The improvement is relatively small with more low risk patients categorized in the intermediate risk group. Application of the adjusted HEART score results in a small fraction of diseased patients who may receive urgent treatment earlier. Hence, medical consumption in non-diseased patients will increase. This regression analysis supports the easy-to-use HEART score with an equal distribution of values given for the five elements.

We investigated the additional value of the cycle exercise ECG in a population of 248 chest pain patients in whom the HEART score was determined. From a statistical point of view, the exercise test may strengthen the diagnostic pathway in selected chest pain patients to some extent. However, the clinical value of the exercise ECG in this setting is still a matter of debate.

Concerning medical consumption and associated costs, we investigated whether the HEART score could be beneficial in reducing this medical consumption. In particular in patients with low HEART scores, hospital admissions and specific diagnostic procedures may be reduced. Avoiding redundant medical care may result in a reduction of iatrogenic damage and cost. Theoretically, annual savings for the national health care system in The Netherlands may exceed ten million Euros.

Another sub study investigated the role of Troponin. Elevated troponin values are almost proof of an ACS. However, the HEART score is applicable for the wide variety of chest pain patients in whom the incidence of ACS is approximately 10%. In this setting, troponin only does not seem to be a strong predictor of short-term MACE, but clinical

data (anamnesis, ECG, age and risk factors) obtained by the physician and results from laboratory testing (troponin) should be used together, combined in the HEART score. In addition, a second troponin measurement results in a slight improvement of the HEART-score to discriminate patients with and without the risk of a cardiac event.

In summary, the HEART score is easy to calculate and applicable to all chest pain patients within one hour after presentation in the ED. Various approaches to improving the HEART score appear to be disappointing.

The studies described in this thesis provide a better view on the approach of chest pain patients in the ED. Our results support the use of the HEART score for early risk stratification of chest pain patients. When accepting a small percentage of false negatives, low risk patients may be discharged without additional workup. However, the question remains what risk of MACE is acceptable. The risk of MACE in patients with low HEART scores is 1.9%, with a negative predictive value of 0.98. There will never be any score that eliminates every risk. In addition, it should be mentioned that our diagnostic MACE definition included ‘revascularization’, an event that is not adverse from a prognosis point of view. It should also be mentioned that the HEART score does not decide anything. The HEART score provides a firm scientific basis to discharge patients from the ED in case of a low score, but that should not inhibit the clinical thinking of the treating physician. A reduction of the use of health care resources may result in a reduction of health care costs.

Implications for the future.

The effects of the implementation of the HEART score will be investigated in a large prospective trial that will include 6000 patients in 10 hospitals in the Netherlands. This study has a stepped wedge design. It is funded by ZonMW and will start including patients in the autumn of 2012. During 15 months, patients presenting with chest pain to the ED of participating hospitals will be included in the study. First, during a period of one month all patients will receive usual care, i.e. without application

of the HEART score. Then during 10 months, all hospitals will sequentially (using randomization) start to apply the HEART score in all chest pain patients. By the end of the study all hospitals will finish with use the HEART score for a minimum of one month. Patients with a HEART score 0-3 will not be admitted to the hospital and patients with a HEART score greater than 3 will be treated according to current guidelines. All patients will be followed for at least three months to assess the study outcome parameters.
In a random subgroup of patients direct medical costs are obtained. Also, actual indirect costs related to productivity loss are obtained. A cost-effectiveness analysis is performed based on differences in cost estimates and quality of life estimates.

Samenvatting

De risicostratificatie bij patiënten met pijn op de borst op de afdeling spoedeisende hulp (SEH) wordt bemoeilijkt door een tamelijk lage diagnostische waarde van de losse elementen van de diagnostiek bij presentatie. De internationale richtlijnen van de samenwerkende cardiovasculaire verenigingen bevelen het gebruik van risicoscores aan om de relatieve argumenten met elkaar in verband te brengen en om patiënten met een laag of hoog risico op cardiovasculaire manifestaties tijdig te herkennen. De HEART-score is speciaal ontwikkeld voor patiënten met pijn op de borst op de SEH en loopt parallel met het klinische redeneren over deze patiënten.

De voorspellende waarde van de HEART-score voor het optreden van belangrijke nadelige cardiovasculaire manifestaties (*major adverse cardiovascular events*; MACE) bij patiënten met pijn op de borst is bepaald in een samenhangende reeks van vier wetenschappelijke onderzoeken. De gegevens van alle 6226 patiënten van deze reeks van vier zijn samengevoegd in één bestand, waarbinnen analyse van subgroepen mogelijk was. De HEART-score blijkt in alle onderzochte subgroepen een krachtige voorspeller van zowel de overleving zonder MACE als het optreden van mogelijk levensbedreigende cardiovasculaire manifestaties. De HEART-score is behulpzaam bij het nemen van betrouwbare beslissingen op de SEH, zonder enig gebruik van röntgen- of katheteronderzoeken. Met de HEART-score kan men binnen een tijdsbestek van een uur vanaf de aankomst van de patiënt in het ziekenhuis zowel (i) een groot aantal laagrisicopatiënten herkennen met een kans op MACE van 1,9%, als (ii) hoogrisicopatiënten met een kans op MACE van ongeveer 50%. Bij middelmatige waarden heeft de HEART-score minder toegevoegde waarde. De HEART-score is een eenvoudige, snelle en betrouwbare voorspeller van de cardiovasculaire einddiagnose bij patiënten met pijn op de borst op de SEH en is daardoor geschikt voor triage.

Oudere risicoscores, zoals de PURSUIT-, TIMI-, GRACE- en FRISC-scores hebben hun fundament in de vorm van grote gegevensbestanden van patiënten met bewezen acute coronaire

syndromen (ACS). Die scores zijn ontwikkeld nadat de voorspellende waarden voor het optreden van MACE (meestal: hartinfarct en overlijden) van onafhankelijke risicofactoren berekend zijn. Deze risicoscores zijn dan ook relatief goed in het herkennen van patiënten met een hoog risico. De soort variabelen die men in deze scores gebruikt zijn echter een nadeel voor het praktische gebruik nabij het ziekenhuisbed. Bovendien hebben deze scores weinig toegevoegde waarde bij de meerderheid van de patiënten met pijn op de borst op de SEH, die geen ACS blijken te hebben. De HEART-score blijkt het aanzienlijk beter te doen dan de TIMI- en de GRACE-score. Zowel het herkennen van laagrisicopatiënten als hoogrisicopatiënten slaagt beter met de HEART-score, die daarmee een hogere diagnostische waarde heeft dan de oude scoresystemen.

Wij hebben onderzocht of de diagnostische waarde van de HEART-score verder verbeterd zou kunnen worden door aanpassingen op basis van multivariate regressieanalyse. Het bleek dat de arbitrair gekozen gewichten van de vijf onderdelen van de HEART-score ruimte lieten voor verbetering. De mogelijke verbetering bleek echter bescheiden te zijn en te leiden tot een verschuiving van een aanzienlijk aantal patiënten van laag naar middelmatig risico. De toepassing van een aangepaste HEART-score zou het voordeel kunnen hebben dat sommige patiënten met cardiovasculaire aandoeningen eerder in behandeling zouden komen, maar daar zou een grotere medische consumptie tegenover staan bij patiënten die uiteindelijk geen aandoening blijken te hebben. De regressieanalyse ondersteunt het gebruik van de eenvoudig in de dagelijkse praktijk toe te passen HEART-score.

De toegevoegde waarde na de berekening van de HEART-score van het inspannings-ECG (met gebruikmaking van de fietsergometer) is geanalyseerd bij 248 patiënten. Vanuit een statistisch oogpunt zou de fietstest de diagnostiek wel enigszins kunnen versterken. Of het inspannings-ECG daarmee een waardevolle toevoeging is voor de kliniek blijft een onderwerp van discussie.

Betreft de medische consumptie en de daaruit voortkomende kosten, hebben wij onderzocht of de HEART-score zou kunnen bijdragen aan besparingen. Vooral bij patiënten met lage HEART-scores liggen besparingen in het verschiet op ziekenhuisopnames en specifiek-cardiologische diagnostiek. Het vermijden van onnodige medische zorgverlening zou ook kunnen leiden tot reductie van iatrogene schade. In theorie zou men door de beleidsconsequenties van lage HEART-scores te aanvaarden, tientallen miljoenen euro's kunnen besparen op de Nederlandse gezondheidszorg.

In een ander deelonderzoek is de bijdrage van de laboratoriumbepaling van het troponinegehalte uitgezocht. Verhoogde troponinewaarden zijn vrijwel bewijzend voor een ACS. De HEART-score dient voor het complete scala van patiënten met acute pijn op de borst, van wie slechts 20% een ACS hebben. Onder deze omstandigheden blijken de troponinewaarden een matige voorspeller te zijn van MACE binnen zes weken; troponine moet worden gebruikt in combinatie met klinische basisgegevens (anamnese, ECG, leeftijd en risicofactoren), zoals in de HEART-score. Verder blijkt dat een tweede troponinebepaling leidt tot een lichte verbetering van de HEART-score in de zin van het onderscheiden van een patiënt met of zonder risico van MACE.

Samengevat: de HEART-score is eenvoudig te berekenen en toepasbaar op alle patiënten met pijn op de borst binnen een uur na aankomst op de SEH. Allerlei manieren om de HEART-score te verbeteren leveren weinig winst op.

De onderzoeken die in dit proefschrift zijn beschreven, geven inzicht in de benadering van patiënten met pijn op de borst op de SEH. Onze resultaten ondersteunen het gebruik van de HEART-score voor de vroege risicostratificatie van deze patiënten. Als een klein percentage valsnegatieven voor lief wordt genomen, kunnen laagrisicopatiënten worden ontslagen zonder aanvullende diagnostiek. Het blijft echter een onderwerp van discussie welk cardiovasculair risico acceptabel is. Het risico op MACE van patiënten met lage HEART-scores bedraagt 1,9%, met een negatieve voorspellende waarde van 0,98. Het is ondenkbaar dat

er ooit een score komt die elk risico voor 100% uitsluit. Daar komt bij dat de revascularisaties deel uit maken van MACE, terwijl deze uitkomst niet bepaald ongunstig is.

Bovendien beslist de HEART-score helemaal niets. Dat doet de behandelend arts, die ook zijn of haar niet-te-kwantificeren klinische blik laat meetellen. De HEART-score biedt een stevig wetenschappelijk fundament om te besluiten geen verder onderzoek te doen bij laagrisicopatiënten of om snel katheterinterventies te doen bij hoogrisicopatiënten, maar dit was niet het onderwerp van het uitgevoerde onderzoek. Bij een besluit van de behandelend arts om laagrisicopatiënten rechtstreeks naar huis te laten vertrekken zal een pluis/niet-pluisgevoel een rol blijven spelen. Beperking van aanvullende diagnostiek zou kunnen leiden tot besparingen op de gezondheidszorg.

Consequenties voor de toekomst

De effecten van de toepassing van de HEART-score zullen worden onderzocht in een groot prospectief onderzoek bij ruim 6000 patiënten in 10 ziekenhuizen in Nederland. Dit onderzoek volgens de '*stepped-wedge design*' wordt gesubsidieerd door ZonMW en zal beginnen met de inclusie van patiënten in het najaar van 2012. Het onderzoek wordt uitgevoerd bij patiënten met pijn op de borst op de SEH of de eerste harthulp. Aanvankelijk worden gedurende 1 maand alle patiënten behandeld volgens de gebruikelijke standaarden zonder toepassing van de HEART-score. Vervolgens zal gedurende tien maanden elke maand één ziekenhuis door middel van loting worden aangewezen om vanaf dat moment de besluitvorming te baseren op de HEART-score. Nadat het laatste ziekenhuis is overgeschakeld, gaan alle tien deelnemende ziekenhuizen door met de toepassing van de HEART-score gedurende 1 maand. In principe worden patiënten met een HEART-score 0 tot 3 niet opgenomen, en patiënten met een HEART-score groter dan 3 worden behandeld volgens de geldende richtlijnen. Alle patiënten worden vervolgd gedurende een periode van minimaal 3 maanden, met vastlegging van de vastgelegde parameters van cardiovasculaire diagnoses.

In een aselect gekozen subgroep van patiënten worden de direct gerelateerde medische kosten in kaart gebracht. Bovendien worden indirecte kosten als gevolg van productiviteitsverlies geregistreerd. Een kosteneffectiviteitanalyse wordt uitgevoerd op basis van verschillen in kostenschattingen en kwaliteit van leven.

Dankwoord

Aan de onderzoeken beschreven in dit proefschrift hebben vele mensen, vaak belangeloos, een bijdrage geleverd. Het is vrij uniek dat een onderzoek met zo weinig financiële middelen in zoveel ziekenhuizen door zoveel enthousiaste mensen wordt uitgevoerd. Voor alle toewijding en dat enthousiasme ben ik erg dankbaar.

HEART was er nooit geweest zonder de unieke samenwerking tussen mij en mijn copromotor Jacob Six. Op 31 dec 2007 is het idee van een validatie onderzoek van de HEART score ontstaan aan Jacob's keukentafel. Geïnspireerd door zijn kennis, ervaring en didactische capaciteiten was ik al snel enthousiast over ons "onderzoekje". De plannen werden gemaakt, de eerste patiëntenlijsten opgezocht en elke zondagochtend stapten we samen in de auto naar Woerden om zelf de codeerformulieren in te vullen. Door de afwezigheid van subsidie hebben we die huiselijke mentaliteit gedurende de afgelopen 5 jaar behouden, hetgeen voornamelijk de charme van het onderzoek en onze samenwerking bestempelde. Vergaderingen vonden thuis plaats, doorgaans vergezeld van een smakelijk diner. En of het nu een eerstejaars student was, een gevestigd cardioloog of de professor, iedereen werd, met veel plezier, onthaald op Sterrenburg.
Hoewel we soms een goede werkplek misten, zorgde deze "thuis-werk"-wijze voor een heel ongedwongen sfeer waarin we ook de ruimte voelden om elkaar te complimenteren en bekritiseren waar nodig. Daardoor heb ik denk ik veel meer dan de gemiddelde promovendus mijn creatieve, didactische en wetenschappelijke capaciteiten kunnen ontwikkelen.
Jacob, dankjewel voor de kansen, (levens)lessen, gastvrijheid, plezier, kritiek, complimenten, vriendschap, maar bovenal het prachtige onderzoek dat je mij geboden hebt.

Al vrij snel in het begin van het onderzoek vonden Jacob en ik enkele toegewijde medeonderzoekers die hun tijd, energie, kennis en financiën in het onderzoek wilden steken.

Pieter Doevendans, mijn promotor, werd al na de eerste resultaten van de pilot studie positief en heeft gedurende vier jaren zijn steun betuigd aan HEART. Zijn enthousiasme voor het onderzoek, kritische blik en connecties met tijdschriften moedigden ons aan.

Hans Kelder heeft ons vanaf het eerste uur ondersteund met de statistische analyses. Tussen al zijn bezigheden door wist hij steeds weer tijd te vinden om de analyses van HEART uit te voeren.

De database voor het prospectieve onderzoek werd gebouwd door Mike Bosschaert. Met verbazing heb ik gekeken naar het gemak waarmee Mike onze ideeën en wensen omzette in een prachtige web-based database, die ons veel monnikenwerk uit handen nam.

Als junior onderzoekers kregen we steun van Thomas Mast en Frederieke van den Akker. Al snel voelden ze zich thuis in het onderzoek en de ongedwongen sfeer en zijn ze vele zondagen met Jacob en mij op pad geweest naar de verschillende ziekenhuizen. Ook hun enthousiasme, doorzettingsvermogen en inzet zijn bewonderenswaardig.
In een latere fase hebben Judith Poldervaart, Hector de Beaufort, Idelès Kaandorp, LaurensJan Jellema en Annelieke Kingma ieder een eigen sub studie op zich genomen. Met veel toewijding en precisie hebben zij de werkzaamheden en analyses van de deelonderzoeken uitgevoerd.

Niels Mäkel hielp ons een website te ontwerpen en onderhouden, zodat HEART ook bekendheid kon krijgen in de rest van de wereld.

Arno Hoes was de *auctor intellectualis* van het implementatieonderzoek van de HEART-score. Het beschrijven van de studieopzet was voor mij leuk en leerzaam. Daarbij is het een vreugdevol idee dat mijn promotieonderzoek zo'n prestigieus vervolg krijgt.

A wonderful piece of co-operation was developed when we met Martin Than, Louise Cullen and Jaimi Greenslade on the internet, physically residing on the other side of the world. This has resulted in the external validation study, the essential part of research that accomplished our program. We hope we may extend this co-operation in the near future.

En dan zijn er nog al die anderen die met hart en ziel hun steun, hulp en geloof in HEART hebben geuit. Gijs Mast, Rolf Veldkamp, Arend Mosterd, Maarten-Jan Cramer, Luc Cozijnsen, Richard Braam, Björn Groenemeijer, Alexander Wardeh, Wouter Tietge, Eugene Buijs, Fabrice Martens, Stefan Monnink, Rene Tio, Peter Tolen, LaurensJan Jellema en Jeroen van Suijlen; dank voor het beoordelen van het studieprotocol, het scoren van ECG's en fietstesten, het invoeren van patiëntgegevens, het bespreken van moeilijke casussen, het uitvoeren van analyses en het lezen van manuscripten. Aanvullende ondersteuning van statistiek en methodologie kregen we van Yvonne Vergouwe, Ewout Steyerberg, Hester van der Zaag, Hester den Ruijter.

Leon Commissaris, Vincent de Reuver en Dick Outenaar van Astellas Pharma wil ik bedanken voor het ontwerpen van een logo, het organiseren van vele besprekingen en presentaties en het ontwikkelen van kaartjes op zakformaat die al in vele doktersjassen terecht zijn gekomen.

Randolf Swinkels en Lennart Stolte van Novartis Pharma wil ik bedanken voor het ontwikkelen van een nieuwe versie van diezelfde zakkaartjes en het organiseren van diverse onderzoeksbijeenkomsten, de contacten met ziekenhuizen en het ontwikkelen van een poster voor de spoedeisende hulp.

Peter Hartingsveldt van Medtronic dank ik voor de genereuze subsidie waarmee ik mijn onderzoek zonder de afleiding van alle nachtdiensten kon afmaken.

Tu Peek-Pel heeft dit onderzoek met warme belangstelling gevolgd en ondersteuning gegeven, waarvoor zeer veel dank.

Menno Gaakeer, al bij onze eerste ontmoeting bleek je een HEART-fan van de eerste orde. Buiten je steun voor en interesse in HEART heb je bovenal ook mij gesteund in mijn keuze voor de SEH-opleiding en het Albert Schweitzer Ziekenhuis in het bijzonder. Ik zie ernaar uit om een van je collega's te worden.

Trudie en Joyce, mijn paranimfen, dank voor jullie onvoorwaardelijke vriendschap, de gezelligheid en mooie momenten die we samen delen. Dank voor jullie steun en hulp rondom de organisatie van mijn promotiedag.

Lieve Geurt en Monique, in de afgelopen 3 jaar hebben jullie mij omarmd. Jullie zijn een fijne, warme en gastvrije schoonfamilie.

Lieve Henk en Elma, pap en mam, ik bof met zulke geweldige ouders die altijd voor mij klaar staan met hun steun en liefde, wijze raad en hulp met klussen of verhuizen. Daarnaast zijn jullie een liefdevolle oppas voor Sophie. Maar bovenal bieden jullie mij een thuis waar ik heel erg graag kom.

Lieve Ben, wat een geluk dat je in mijn leven kwam en bleef. We maakten een vliegende start gevolgd door een hectische reis, toch bleef jij steeds weer mijn in rots in de branding. Nu is er tijd voor rust. Laten we nog meer gaan genieten van ons leven samen, onze liefde en onze prachtige dochter Sophie.
"*Geef me liefde, geef me rust, laat me nooit meer gaan. Jij geeft sinds jouw eerste kus, zin aan mijn bestaan*".

Curriculum Vitae

De auteur van dit proefschrift werd geboren op 14 december 1979 in Eindhoven. Na het afronden van het Stedelijk Gymnasium te Breda in 1998 begon zij aan de studie Geneeskunde aan de universiteit van Maastricht. Gedurende haar studie werkte zij als telefonisch triagist op de huisartsenpost en schreef zij mee aan de medische inhoud van het programma e-Xpert Triage. In 2003 werkte zij gedurende een jaar als student-assistent aan de studie “Genetica en zoutgevoeligheid van hypertensie” onder leiding van Bram Kroon. De interesse voor klinisch onderzoek werd gewekt. Toch deed zij eerst twee jaar klinische ervaring op als arts-assistent Cardiologie in Heerlen voordat zij de overstap maakte naar (promotie)onderzoek. Zij werkte twee jaar als arts-onderzoeker aan de PERMIT studie bij de nucleaire geneeskunde in het Antonius ziekenhuis in Nieuwegein onder leiding van Fred Verzijlbergen. In diezelfde periode startte zij met Jacob Six aan de HEART studie. Dit onderzoek werd uiteindelijk haar promotieonderzoek. Gedurende 3 jaar heeft zij in verschillende ziekenhuizen nachtdiensten gedraaid als ANIOS cardiologie om haar klinische ervaring te behouden én het HEART onderzoek in de praktijk te kunnen toetsen. Daarnaast was zij van 2007 tot 2011 docent medische vakken op de Hogeschool in Utrecht. In maart 2012 heeft zij de overstap gemaakt naar de Spoedeisende hulp Geneeskunde in het Albert Schweitzer ziekenhuis in Dordrecht. In 2011 is zij getrouwd met Ben van Leeuwen en samen hebben ze een dochter, Sophie.

List of publications

1. **Old inferior wall infarction?** BE Backus, T Lenderink, AJ Six. *Netherlands Heart Journal, 15(7): 271-272*
2. **Chest pain in the emergency room:** value of the HEART score. AJ Six, BE Backus, JC Kelder. *Netherlands Heart Journal, 16(9): 191-196*
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5. **The HEART score for chest pain patients at the emergency room.** B.E. Backus, A.J. Six, J.C. Kelder, T.P. Mast, F. Van Den Akker, P.A. Doevendans. *Eur Heart J 2009;30 (suppl 1); page 312 (abstract 1956)*
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