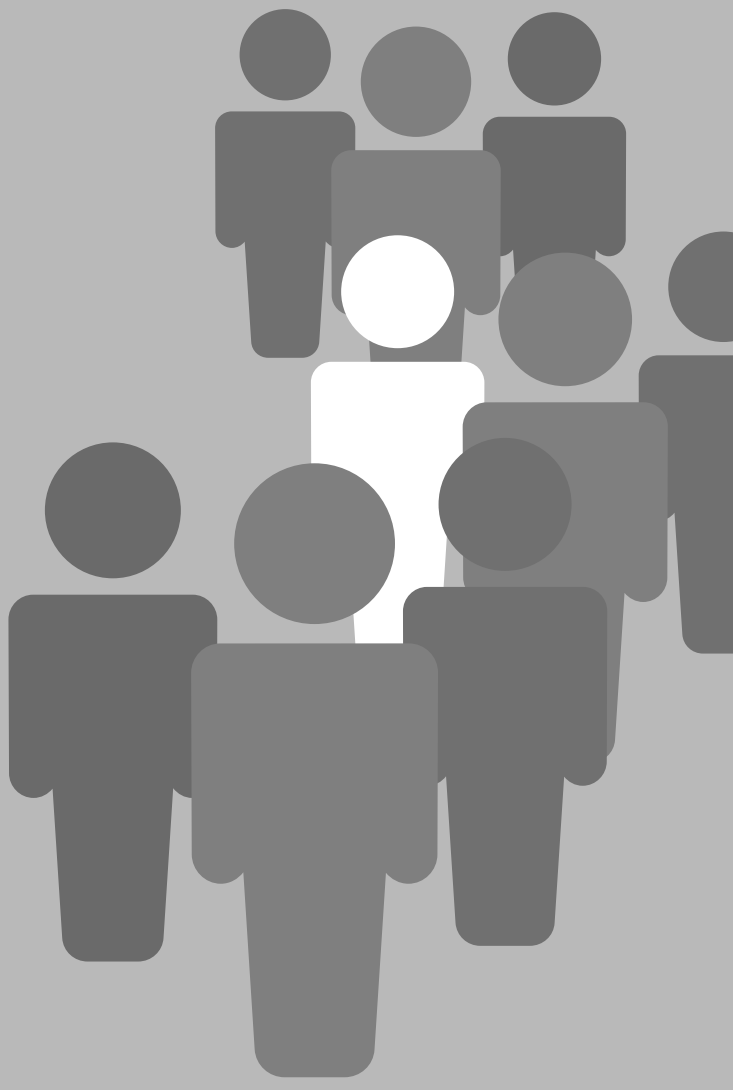
Risk stratification in chest pain patients



Judith Poldervaart

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Risk stratification in chest pain patients

Risicostratificatie in 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,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 18 februari 2016 des middags te 2.30 uur

door

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geboren op 21 januari 1986 te Hilvarenbeek

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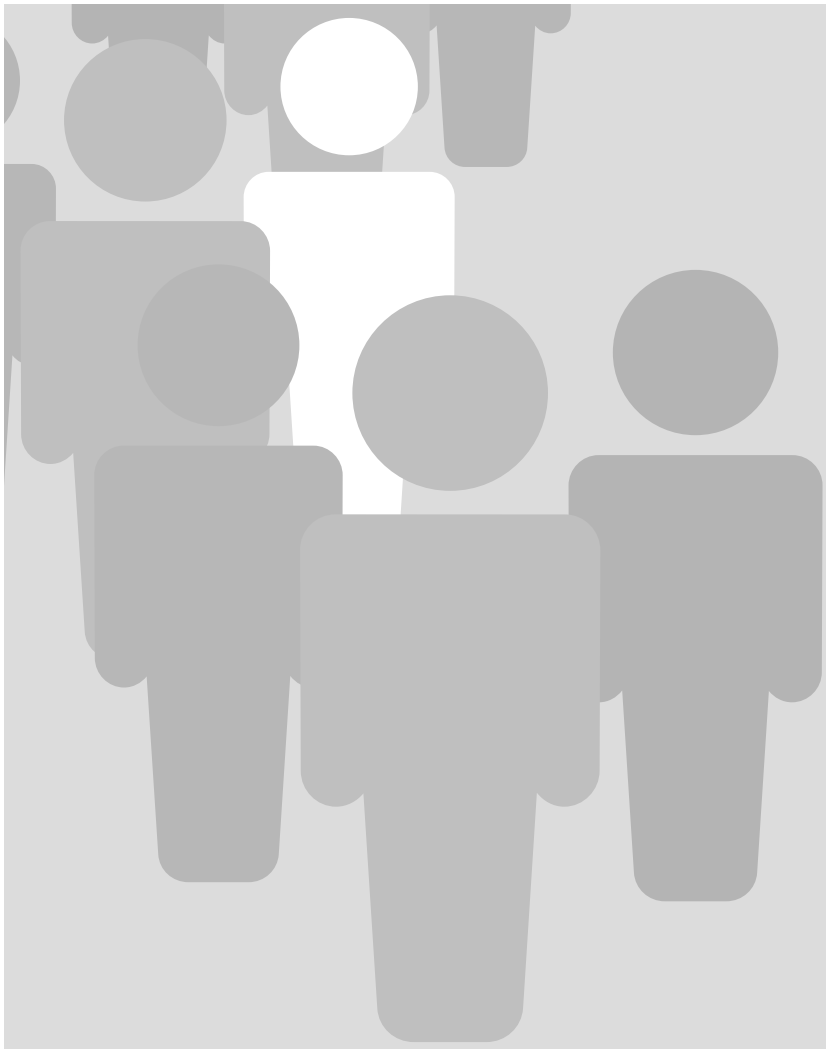
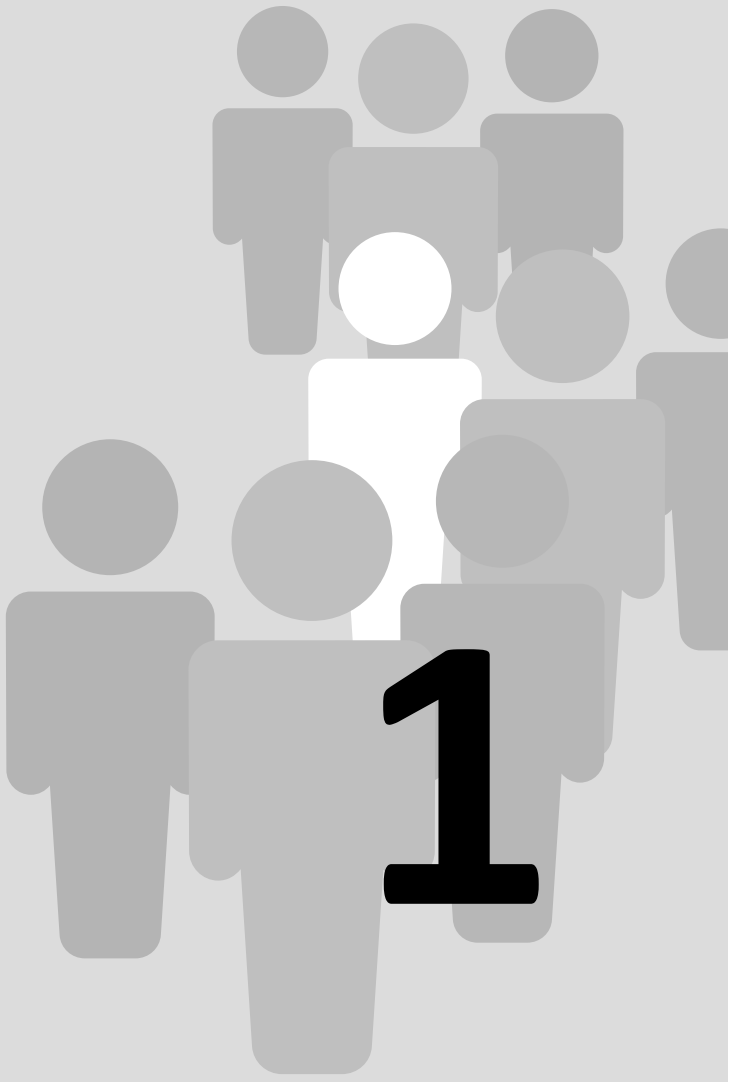
Copromotoren: Dr. J.B. Reitsma
Dr. A.J. Six

"Medicine is a science of uncertainty and an art of probability"
William Osler (1849 – 1919)

CONTENTS



General introduction



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Clinical case

A 48-year old man presents to the emergency department (ED) at 4 pm with chest pain, which started four hours ago when reading the newspaper at home. He has no palpitations or shortness of breath. The attending physician takes a full history, performs a physical examination, and orders an electrocardiography (ECG) as well as routine laboratory tests, including a high sensitive cardiac troponin (hs-cTn) measurement. All tests are within the normal range. Given the age, atypical history, normal ECG and negative troponin measurement, the risk for acute coronary syndrome (ACS) is very low for this patient. However, the physician orders a stress bicycle test for his patient, just to be sure. Since it is now after office hours, the patient has to stay overnight, to undergo his stress test in the morning. The next morning, the stress test is without abnormalities, but during the test, the patient did not achieve the maximum heart frequency required to have a conclusive test. The physician reexamines the patient: no further episodes of chest pain occurred and troponin levels are still normal. The physician wonders about the risks of discharging the patient without a conclusive stress test. He decides to perform a nuclear scan, which takes two separate days to perform, one for resting images and one for stress images. The nuclear scan shows no signs of cardiac ischemia or other cardiac abnormalities. The patient is discharged, after three days of admission.

Chest pain

In 2014 the Dutch public was put to vote by the Dutch Heart Foundation, asking which research themes need to be prioritized. One of the themes voted most for was the theme "*earlier recognition of cardiovascular disease*"[1]. Every day, 5 to 10 patients present with complaints of chest pain to an ED in the Netherlands[2]. In 20% of the cases, the underlying cause is an ACS; i.e. acute myocardial infarction (AMI) or unstable angina (UA)[3], requiring prompt admission and treatment. This presents the treating physician with a dilemma: the majority of patients presenting with chest pain do not have any life-threatening condition, but missing an ACS can have fatal consequences.

Current practice

Current practice differs between countries and even hospitals, but typically is rather defensive: up to 75% of patients is admitted to the hospital for observation and receives additional testing[4]. This is a time-consuming and costly strategy. Moreover, it implies unnecessary exposure of low-risk patients to the risk of complications due to some these diagnostic procedures (such as coronary angiography). International cardiac guidelines recommend a thoroughly taken history and physical examination, performing serial ECGs and serial testing of hs-cTn[5]. Still, there is a considerable number of patients with a non-conclusive or normal ECG and normal serial troponin test, who are at risk of developing an ACS. In Canada, which

has a comparable health care system to the Netherlands, the reported proportion of missed ACS events vary from 4.6% up to 6.4%[6]. These missed patients are at risk for acute cardiac death. This is especially the case with unstable angina, which per definition is devoid of cardiac damage and therefore cardiac biomarkers. Evidently, further risk stratification in this group of patients is necessary to reduce the number of false-negatives, without increasing the number of unnecessary admissions and diagnostic procedures.

Clinical prediction rules

Over the years, many diagnostic strategies have been developed[7-14]. One of these strategies is the use of a clinical prediction rule, which is designed to guide a physicians' decision making, preferably at the bedside[15]. Clinical prediction rules consist of variables including history, physical examination and frequently also basic diagnostic tests, such as laboratory tests[16]. In the case of patients with chest pain, it can be used to estimate the risk of short-term major adverse cardiac events (MACE). Most prediction rules for ACS consist of readily available information from history taking, physical examination, ECG and cardiac biomarkers[7-14].

The HEART score

One of these clinical prediction rules for chest pain patients is the HEART score, developed in 2007 in the Netherlands by Jacob Six and Barbra Backus. The HEART score incorporates the clinical elements of History (H), ECG (E), Age (A), Risk factors (R) and Troponin (T), and appreciates each with 0, 1 or 2 points, resulting in a total score between 0 and 10 (Figure 1). Most importantly, each individual HEART score provides a physician with a formal recommendation whether a patient should be admitted or not. The HEART score has been extensively validated in different countries and settings[14,17-24]. In a pooled analysis of 6,174 patients, the occurrence of MACE in low-risk patients (HEART score below 3) was 1.6% (95% CI: 1.05-2.15)[25]. In addition, a small pilot study showed that when adhering to the HEART score, low-risk patients could be discharged from the ED after initial evaluation, improving patient flow at the ED and reducing the number of unnecessary diagnostic procedures and observations[20,26].

The next step: impact evaluation and implementation

After derivation and extensive internal and external validation, a clinical prediction rule is ready for the next step in model development: assessment of its impact in daily practice[27]. When really used as proposed and implemented in daily practice, is the clinical prediction rule yielding its promised safety and benefits? In practice, however, such an impact study is rarely done. A review by Hess and colleagues concluded that "Current prediction rules for ACS have substantial methodological limitations and have not been successfully implemented in the clinical setting"[28]. When performing an impact study, various outcomes are taken should

into account: not only safety (typically false-negatives), but also effects on quality of life, direct and indirect costs, and, in the case of the HEART score, patient flow at the ED. The key question is whether application and adherence to the HEART score in daily practice results in a significant reduction of patient burden, hospital admissions and health care costs, while not causing an increase in the occurrence of MACE (the latter as a measure of safety).

Figure 1. The HEART score for chest pain patients

HEART score for chest pain patients

History (Anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-deviation	2	
	Non-specific repolarisation disturbance / LBBB / PM	1	
	Normal	0	
Age	≥ 65 years	2	
	45 – 65 years	1	
	≤ 45 years	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 for atherosclerotic disease:

Hypercholesterolemia	Cigarette smoking
Hypertension	Positive family history
Diabetes Mellitus	Obesity (BMI>30)

Main objectives of this thesis

This thesis focusses on accurate and early detection of ACS in chest pain patients. The objectives of this thesis were two-fold. First, we aimed to investigate whether the validated HEART risk score is a safe and cost-effective method when evaluating chest pain patients at the ED, and whether it outperforms the two other worldwide commonly used risk scores (TIMI score and GRACE score) in terms of safely identifying the largest proportion of low-risk patients. Second, we evaluated the added diagnostic value of two other tests, namely stress bicycle testing and novel cardiac biomarkers in chest pain patients.

Outline of this thesis

In **Chapter 2** we performed an additional analysis on the prospective validation cohort of the HEART score and compared the TIMI score and the HEART score in terms of medical consumption. In Chapters 3 and 4 the design and results of the HEART-Impact trial are presented. In **Chapter 3,** we present the design of the HEART-Impact trial, which is a stepped wedge, cluster randomized trial in patients presenting with chest pain in 9 hospitals in the Netherlands. In **Chapter 4** the findings of the HEART-Impact trial are reported. In this pragmatic trial we compared "HEART care" with "usual care" in terms of safety, use of medical resources and costs. The HEART care included a calculation of the HEART score in every individual patient and a recommendation of subsequent patient management. In **Chapter 5** we compare the diagnostic performance of the HEART score with two other commonly used scores, namely the GRACE score and the TIMI score, in the population included in our HEART impact trial. In **Chapter 6** we investigated the diagnostic value (on top of current practice, namely history taking, cardiac history, risk factors and ECG) of novel cardiac biomarkers, such as copeptin and myoglobin, for diagnosing ACS in chest pain patients. In **Chapter 7** we evaluated the diagnostic value of stress bicycle testing, the most commonly used diagnostic procedure in chest pain patients presenting at the ED. In **Chapter 8** we discuss the implications of the findings of the studies presented in this thesis for the management of patients presenting with chest pain.

REFERENCES

1. https://www.hartstichting.nl/onderzoek
2. http://www.toolkitvtv.nl/inhoud/indicatoren-en-bronnen/zorg/hap-en-seh-ziekenhuis/
3. Lee TH, Goldman L. Evaluation of the patient with acute chest pain. N Engl J Med 2000, 342:1187–1195.
4. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart. 2005;91(2):229-30.
5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2015 Aug 29. pii: ehv320.2015.
6. Christenson J, Innes G, McKnight D, Boychuk B, Grafstein E, Thompson CR, et al. Safety and efficiency of emergency department assessment of chest discomfort. CMAJ 2004;170:1803-7.
7. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. The GRACE investigators. Predictors of hospital mortality in the global registry of acute coronary events. Archives of internal medicine. 2003;163: 2345-53.
8. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook G, et al. The Manchester acute coronary syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. Heart. 2014;100(18): 1462-8.
9. Antman EM, Cohen M, Bernink PJLM, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI; a method for prognostication and therapeutic decision making. JAMA. 2000;284:835-42.
10. Christenson J, Innes G, McKnight D, Thompson CR, Wong H, Yu E, et al. A clinical prediction rule for early discharge of patients with chest pain. Annals of emergency medicine. 2006;47: 1-10.
11. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med. 2012;172(16):1211-8.
12. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med. 2012;366(15):1393-403.
13. Than M, Cullen L, Reid CM, Lim SH, Aldous S, Ardagh MW, et al. A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. Lancet. 2011;377(9771):1077-84.
14. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J 2008;16:191-6.
15. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA 2000;284:79-84.
16. Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. Ann Emerg Med 1999;33:437-47.
17. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room; a multicenter validation of the HEART score. Crit Path Cardiology 2010;9:164-169.
18. Backus BE, Six AJ, Kelder JC, Bosschaert MAR, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol. 2013;168(3):2153-8.
19. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART Score for the Assessment of Patients With Chest Pain in the Emergency Department: A Multinational Validation Study. Crit Pathways in Cardiol 2013;12:121–126.
20. Mahler SA, Hiestand BC, Goff DC Jr, Hoekstra JW, Miller CD. Can the HEART score safely reduce stress testing and cardiac imaging in patients at low risk for major adverse cardiac events? Crit Pathw Cardiol. 2011;10(3):128-33.

21. Mahler SA, Miller CD, Hollander JE, Nagurney JT, Birkhahn R, Singer AJ, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. Int J Cardiol. 2013;168(2):795-802.
22. Mahler SA, Riley RF, Hiestand BC, Russell GB, Hoekstra JW, Lefebvre CW, et al. The HEART Pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. Circ Cardiovasc Qual Outcomes. 2015;8(2):195-203.
23. Melki D, Jernberg T. HEART score: a simple and useful tool that may lower the proportion of chest pain patients who are admitted. Crit Pathw Cardiol. 2013;12(3):127-31.
24. Carlton EW, Khattab A, Greaves K. Identifying Patients Suitable for Discharge After a Single-Presentation High-Sensitivity Troponin Result: A Comparison of Five Established Risk Scores and Two High-Sensitivity Assays. Ann Emerg Med. 2015 Jul 29. pii: S0196-0644(15)00583-1.
25. Unpublished pooled analysis of data 18 & 19.
26. Six AJ, Backus BE, Kingma A, Kaandorp SI. Consumption of diagnostic procedures and other cardiology care in chest pain patients after presentation at the emergency department. Neth Heart J. 2012;20(12):499-504.
27. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ. 2009 Jun 4;338:b606.
28. Hess EP, Thiruganasambandamoorthy V, Wells GA, Erwin P, Jaffe AS, Hollander JE, et al. Diagnostic accuracy of clinical prediction rules to exclude acute coronary syndrome in the emergency department setting: a systematic review. CJEM. 2008;10(4):373-82.

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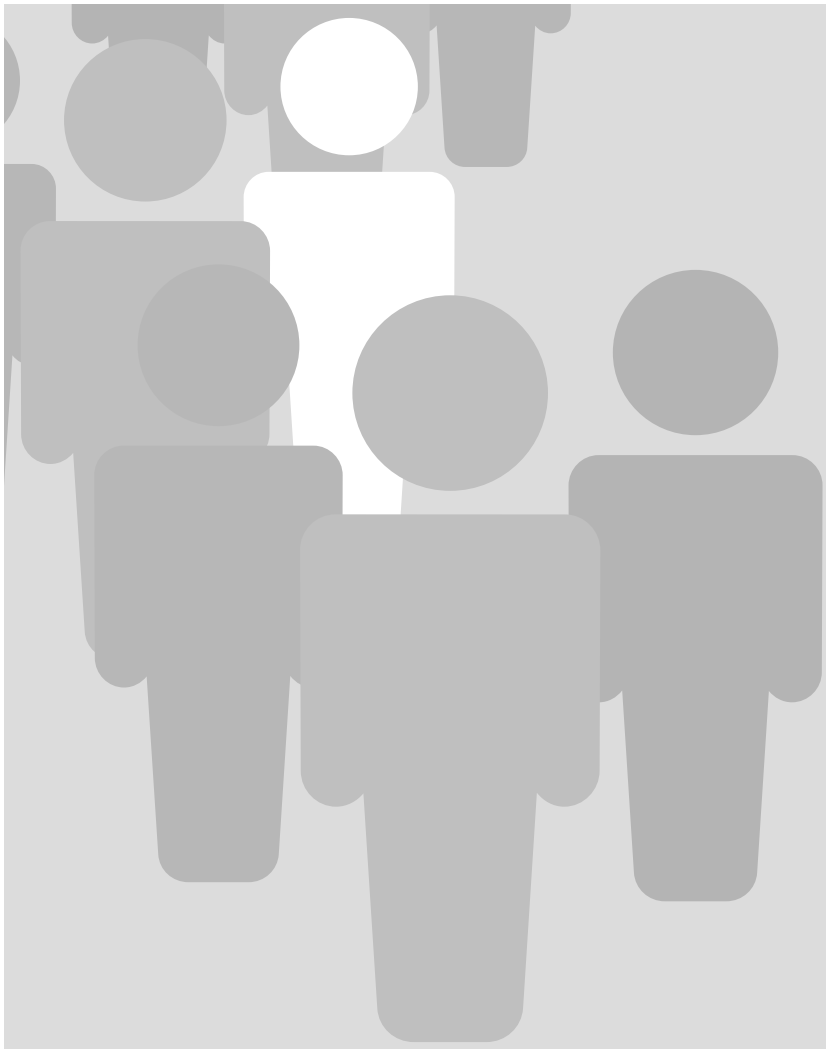
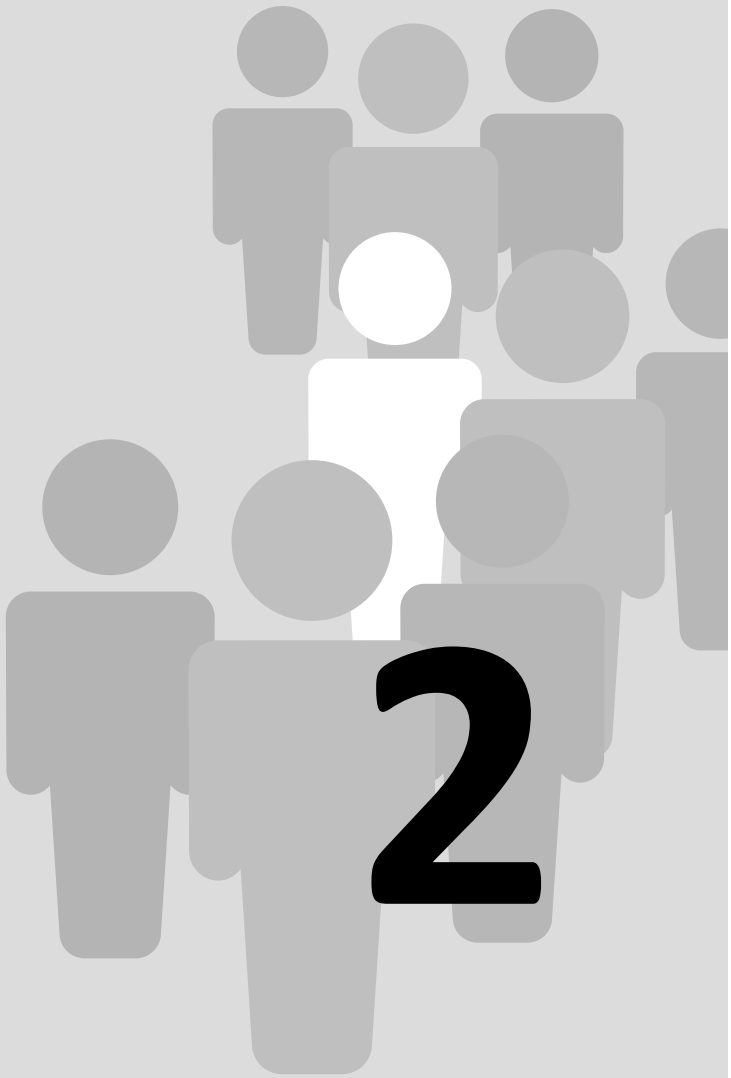


Medical consumption compared for TIMI and HEART score in chest pain patients at the emergency department

A. Nieuwets, J.M. Poldervaart, J.B. Reitsma, S. Buitendijk, A.J. Six, B.E. Backus, P.A. Doevendans, A.W. Hoes

Submitted



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ABSTRACT

Objective: We investigated which risk score (TIMI score or HEART score) identifies the largest population of low-risk patients at the emergency department (ED). Furthermore, we retrospectively calculated which score resulted in the largest decrease in medical consumption if patients would have been discharged from the ED.

Methods: We performed analyses in two hospitals of the multicenter prospective validation study of the HEART score. Chest pain patients presenting to the ED were included and information was collected on major adverse cardiac events (MACE) and on hospital admissions and diagnostic procedures within 6 weeks. The TIMI and HEART score were calculated.

Results: We analysed 640 patients (59% male, mean age of 60, cumulative incidence of MACE 17%). An estimated total of €763,468 was spent during follow-up on hospital admission and diagnostic procedures. 256 (40%) patients had a HEART score of 0 to 3 and were considered low-risk, a total of €64,107 was spent on diagnostic procedures and hospital admission after initial presentation in this group. In comparison, 105 (16%) patients with TIMI score of 0 were considered low-risk, with a total of €14,670 spent on diagnostic procedures and initial hospital admission costs.

Conclusions: The HEART score identifies more patients as low-risk compared to the TIMI score, which may lead to a larger reduction in diagnostic procedures and costs in this low-risk group. Future studies should prospectively investigate whether adhering to the HEART score in clinical practice and early discharge of low-risk patients is safe and leads to a reduction in medical consumption.

BACKGROUND

Each year, an estimated 6% of presentations at emergency departments (ED) are attributed to symptoms suspicious of acute coronary syndrome (ACS)[1,2]. Of all these patients, the majority has chest pain due to non-cardiac causes and only 15-20% of patients have an ACS[3]. Differentiating between low and high-risk patients for ACS remains a diagnostic challenge, since a normal electrocardiogram (ECG) and initially negative biomarkers do not exclude ACS. Therefore, the majority of low-risk patients are currently admitted to the hospital to undergo stress testing, regardless of low pre-test probability. However, often results of these performed tests are normal[4]. The question remains whether this conservative approach leads to better clinical outcomes for patients and there is discussion on optimal management in patients who are deemed safe to discharge from the ED[5].

Several risk stratification tools and prediction models have been developed over time. Currently, international cardiac guidelines recommend the use of a risk score for risk stratification[6-7]. The current study investigates two of these risk scores, namely the TIMI score and the HEART score. Firstly, the Thrombosis In Myocardial Infarction (TIMI) risk score is used to stratify risk in chest pain patients admitted to the cardiac care unit (CCU) and can be used to predict 30-day outcomes of mortality, myocardial infarction (MI) and severe recurrent ischemia requiring urgent revascularization[8,9]. The TIMI score is composed of 7 elements as shown in Table 1. It is one of the two risk scores that are implemented in current international guidelines and well-known by most clinicians[10]. Secondly, the HEART score was developed in 2007 and has been validated to stratify the risk of short-term adverse cardiac events in chest pain patients at the ED[9,11-16]. The HEART score is an acronym for History, ECG, Age, Risk factors and Troponin. These components can be rated 0, 1 or 2 points each and results in a total HEART score between 0 and 10, as shown in Table 2. It has been specifically developed for chest pain patients and previous prospective studies indicated the HEART score as valid for patient stratification[9,11,14,15,17-19].

Although both risk scores have been validated, they are mostly not yet actively used[3,8,9,11,12,14-24]; that is, no policy decision is made based on the individual risk score of a patient. Furthermore, none of these previous studies mentioned secondary outcome measurements such as clinical course or medical consumption. A pilot study of 122 patients by Six et al. analysed medical consumption of chest pain patients with a HEART score at the ED[17]. It concluded that, if the HEART score would be routinely applied on chest pain patients, diagnostic pathways for low-risk patients could be shortened which could lead to cost reduction. However, these were small numbers in a small non-academic hospital.

Our goal is to investigate the medical consumption in the low-risk TIMI and HEART score categories. Furthermore, we assessed which risk score is more efficient in identifying the largest number of low-risk patients, without compromising safety.

Table 1. The TIMI (thrombosis in myocardial infarction) score for unstable angina/NSTEMI

Age ≥ 65 years	0
	1
≥ 3 risk factors for CAD	0
	1
Known CAD	0
	1
Aspirin use in past 7 days	0
	1
Recent severe angina	0
	1
Elevated cardiac markers	0
	1
ST deviation ≥ 0.5 mm	0
	1
TOTAL	0-7

CAD: Coronary artery disease, NSTEMI: non-ST-segment elevation myocardial infarction

Table 2. The HEART score for chest pain patients

History	Highly suspicious	2
	Moderately suspicious	1
	Slightly or non-suspicious	0
ECG	Significant ST-depression	2
	Nonspecific repolarization disturbance	1
	Normal	0
Age	≥65 years	2
	>45-<65 years	1
	≤45 years	0
Risk factors	≥3 risk factors, or history of atherosclerotic disease	2
	1 or 2 risk factors	1
	No risk factors known	0
Troponin	≥3 x normal limit	2
	>1-<3 normal limit	1
	≤ Normal limit	0
Total		0-10

ECG: electrocardiogram

METHODS

Study population

This is an additional analysis of 680 patients in two hospitals, using the data of a multicenter prospective validation study in 10 hospitals of the HEART score, which included a total of 2,388 patients between 2008 and 2009[15]. The ethics committees of all participating hospitals approved the study. Since it was an observational study and patients received standard care, at that time informed consent procedures were waived. Patients were informed of the registration of data and the follow-up policy and data was processed anonymously. Any patient with acute chest pain admitted to the (cardiac) ED was eligible, regardless of age or pre-hospital suspicion. Patients with ST-elevation myocardial infarction (STEMI) were immediately taken to the coronary intervention room, and therefore excluded. Two hospitals were chosen for this sub analysis on diagnostic procedures as it was anticipated that for these hospitals patient information of sufficient quality would be available. The first is a general hospital with a large specialised cardiology department, the second an academic hospital. Both are intervention centres and perform percutaneous coronary intervention (PCI) and coronary artery bypass surgery (CABG).

Calculation of the TIMI and HEART score

ED residents of participating hospitals were instructed to fill out the Case Record Form (CRF), which consisted of patient history, cardiovascular risk factors, medication, physical examination and past medical history. Laboratory results, including conventional Troponin I or T, and the admission ECG were added to the CRF. The ECG was blindly classified afterwards by independent, experienced cardiologists. The HEART score was developed in 2007 and predicts the 6-week incidence of major adverse cardiac events (MACE), stratifying patients into a low-risk (HEART score 0-3), intermediate-risk (4-6) and high-risk (7-10) group[12,15,16]. The incidence of MACE in the previous validation studies has been 1.7% in low-risk patients, 16.6% in intermediate-risk patients, and 50.1% in high-risk patients[15]. The classification into the different risk categories can be used to make a direct clinical decision for further patient evaluation. In the current study, the HEART score was calculated by the resident at the ED, without actively using the score for further management. Each of the 5 elements in the HEART score were given 0, 1 or 2 points, resulting in a score between 0 and 10, see Table 2. The TIMI score was developed in 2000 for prediction at the CCU for 30-day outcomes of mortality, myocardial infarction (MI) and severe recurrent ischemia requiring urgent revascularization, with the following occurrence rates: 4.7% for TIMI 0/1, 8.3% for 2, 13.2% for 3, 19.9% for 4, 26.2% for 5 and 40.9% for 6-7[8]. Only a TIMI score of 0 seems to identify patients to be safely discharged home from the ED without further testing[19-23]. In the current study, an algorithm was devised to calculate for the TIMI score automatically from admission

data, without interpretation by the investigators and blinded for the outcome. The score consists of 7 elements, and each of the 7 elements was given 0 or 1 point, resulting a total score between 0 and 7, see Table 1.

Outcome measures

6-week occurrence of MACE

Information on the primary outcome of MACE was already collected during the original study[15]. The definition of MACE consisted of AMI, PCI, CABG, stenosis managed conservatively, and death due to any cause. The duration of follow-up was six weeks in all patients. The diagnosis of AMI was diagnosed by an adjudication committee according to the applicable guidelines at that time[10]. Further information on definition and assessment of MACE can be found in the main publication[15].

Occurrence of MACE in low-risk group

Since we were particularly interested in the low-risk population, low-risk was defined as missed MACE in less than 5% of all patients with MACE in each total score. For the HEART score this resulted in a low-risk group of patients with a score from 0 to 3. For the TIMI score this low-risk group consisted of patients with a TIMI score of 0.

Admission, re-admission, ED revisits, out-patient clinic visits and diagnostic procedures

Additionally, information on whether or not patients were admitted after the initial presentation, length of admission, re-admissions, ED revisits, out-patient clinic visits and diagnostic procedures within six-weeks after initial presentation was collected. All information was retrieved from electronic patient files. Information on the following diagnostic procedures was collected: bicycle stress testing with exercise ECG, myocardial scintigraphy, cardiac MRI, coronary computed tomography angiography (CCTA) and coronary angiography (CAG). Standard (thoracic) CT-scans were not included, since these were mostly requested in the context of pulmonary disease.

Costs

Costs of diagnostic procedures were based on rates as provided by a university medical centre[28]. These costs were up to date as of January 1st, 2015. Costs of hospital admission and ED visits were based on Dutch guidelines for medical cost analysis[25].

Statistical analysis

Continuous variables are presented as means (± standard deviation, SD) or medians (interquartile range, IQR), while categorical variables are presented as numbers (percentage). From contingency tables, the incidence of MACE and distribution of the use of health care resources were extracted. Of the incidence of MACE the corresponding 95% confidence

intervals (CI) were calculated. All analyses were performed using Statistical Package for the Social Sciences for Windows 20.0 (SPSS Incl. Chicago, Illinois).

RESULTS

Study population

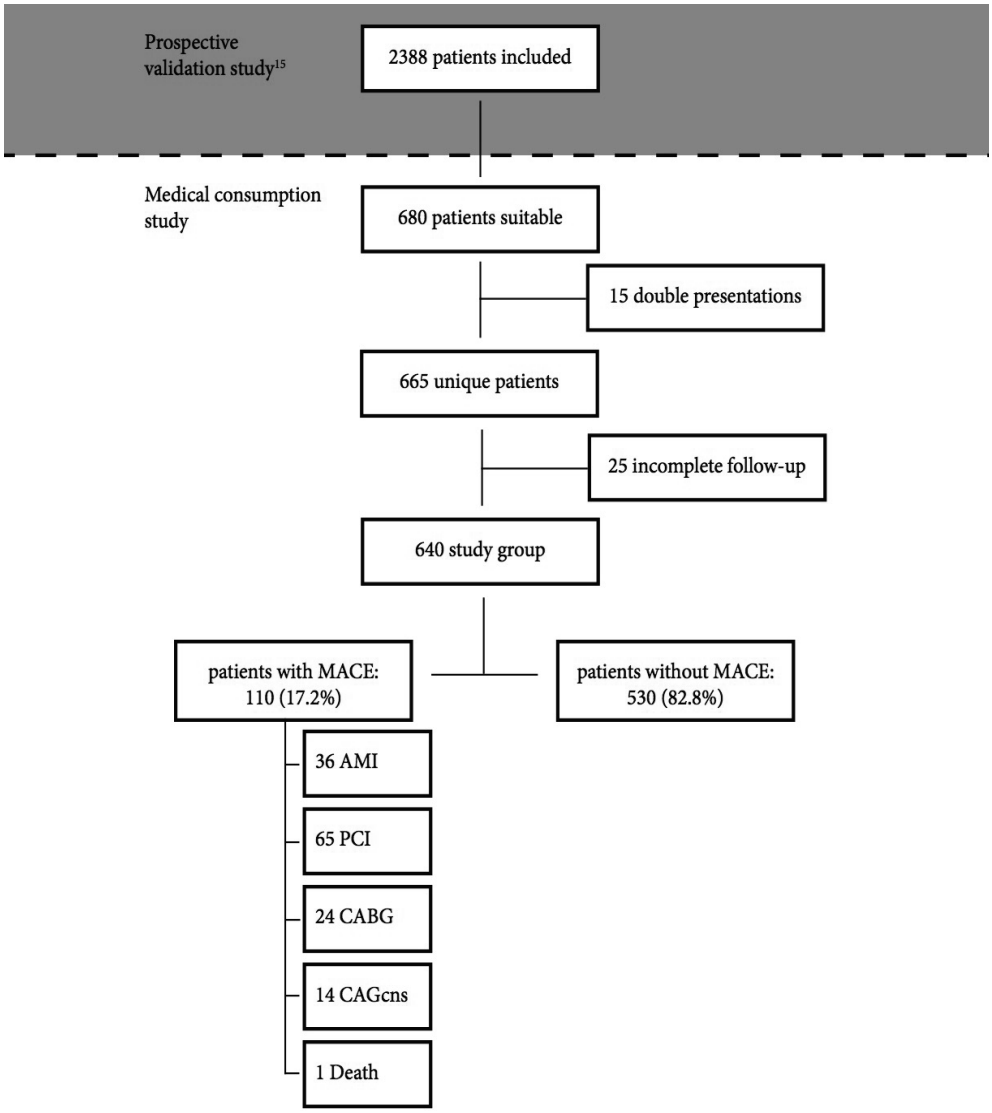
The current study included 680 patients of two hospitals (28.5% of the initial study population). Attempts were made to track down follow-up data for patients receiving their follow-up in different hospitals than the study hospitals, however, in 25 patients (3.7%) we were unsuccessful and thus these patients were lost to follow-up. Additionally, 15 (2.2%) patients were included twice in the original study and we considered only their first presentation. For an overview of patient selection with inclusion and exclusion, see Figure 1. Eventually, 640 patients remained for analysis. Mean age was 60 years and 59% was male. Baseline characteristics are depicted in Table 3.

Table 3. Baseline characteristics

	Total		Patients without MACE		Patients with MACE	
	mean/n	SD/%	mean/n	SD/%	mean/n	SD/%
Demographics						
Study group	640		530	83%	110	17%
Age in years	60.0	15	59	16	67	11
Male	376	59%	298	56%	81	74%
Vital signs at presentation						
Heart rate	76.5	19	77	19	76	17
Systolic blood pressure	139.0	22	138	21	142	23
Diastolic blood pressure	81.9	34	82	37	81	14
Cardiovascular risk factors						
Diabetes Mellitus	105	16%	84	16%	4	4%
Hypertension	277	44%	225	42%	54	49%
Hypercholesterolemia	235	37%	183	35%	55	50%
Smoking	207	32%	167	32%	40	36%
Family history of CVD	254	40%	202	38%	52	47%
Obesity	131	21%	107	20%	24	22%
History of cardiovascular disease						
Myocardial infarction	118	19%	89	17%	31	28%
CABG	60	9%	43	8%	18	16%
PCI	131	21%	97	18%	35	32%
CVA	241	38%	181	34%	63	57%
PAD	23	4%	16	3%	7	6%
Mean HEART score	4.2	2	4	2	7	2
Mean TIMI score	2.4	2	2	2	4	1

n: number, SD: standard deviation, CV: cardiovascular, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, CVA: cerebrovascular accident, PAD: peripheral arterial disease, ECG: electrocardiogram

Figure 1. Patient flow chart



MACE: major adverse cardiac events, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary arterial bypass grafting; CAGcns: coronary angiography with significant stenosis, conservatively treated

Six-week occurrence of MACE

A total of 110 (17.2%) patients out of the 640 were diagnosed with MACE. Figure 1 and Table 4 give an overview of the distribution of the different conditions within MACE. Most common was the performance of PCI in 65 patients (59.1%). A diagnosis of AMI was made in 36 patients (32.7%), 24 patients received a CABG (21.8%) and 14 patients (12.7%) had a stenosis on CAG that could be managed conservatively. One patient died (0.9%), with a HEART score of 10 and a TIMI score of 7. This 85-year old male with NSTEMI was managed conservatively because of high age and comorbidity, however developed new cardiac ischemia and died shortly after.

Occurrence of MACE across risk score categories

A patient was defined as low-risk when MACE cumulative incidence of missed MACE was less than 5% of all 110 patients with MACE (Table 4). This resulted in a low-risk group of patients with a HEART score of 0 to 3 (n=256, cumulative MACE incidence in this low-risk group: 1.6%; 95% CI: 0.6 to 4.0%) or TIMI score of 0 (n=105, cumulative MACE incidence in this low-risk group: 0%; 95% CI: 0 to 3.5%).

Table 4. Components of MACE for each TIMI and HEART score and cumulative frequency of all patients with MACE and all patients in risk group

TIMI		Components of MACE*					Cumulative frequency of all patients with MACE and all patients in risk group			
	N patients	AMI	PCI	CABG	CAG cons	Death	Total patients with MACE	Cum. frequency of all patients with MACE	Cum. frequency MACE of all patients in risk group	Cumulative N patients
0	105	0	0	0	0	0	0	0%	0%	105
1	125	2	7	0	0	0	7	6.4%	3.0%	230
2	120	7	9	3	1	0	16	20.1%	6.6%	350
3	112	7	14	5	6	0	24	42.7%	10.2%	462
4	98	5	11	5	3	0	20	60.9%	12.0%	560
5	55	11	16	7	3	0	29	87.3%	15.6%	615
6	23	3	8	3	1	0	12	98.2%	17.0%	638
7	2	1	0	1	0	1	2	100%	17.2%	640
Total	640	36	65	24	14	1	110	100%	17.2%	640

HEART		Components of MACE*					Cumulative frequency of all patients with MACE and all patients in risk group			
	N patients	AMI	PCI	CABG	CAG cons	Death	Total patients with MACE	Cum. frequency of all patients with MACE	Cum. frequency MACE of all patients in risk group	Cumulative N patients
0	18	0	0	0	0	0	0	0%	0%	18
1	46	0	0	0	0	0	0	0%	0%	64
2	85	1	1	0	0	0	1	0.9%	0.7%	149
3	107	0	2	1	0	0	3	3.6%	1.6%	256
4	105	2	6	0	2	0	8	10.9%	3.3%	361
5	103	2	9	4	0	0	15	24.5%	5.8%	464
6	76	8	12	7	1	0	24	46.4%	9.4%	540
7	56	11	14	8	9	0	31	74.5%	13.8%	596
8	29	5	14	2	2	0	18	90.9%	16.0%	625
9	10	4	6	0	0	0	6	96.4%	16.7%	635
10	5	3	1	2	0	1	4	100%	17.2%	640
Total	640	36	65	24	14	1	110	100%	17.2%	640

n: number of patients, MACE: major adverse cardiac events, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary arterial bypass grafting, CAG cons: CAG conservatively treated. * total components of MACE can exceed the total number of patients with MACE, since 1 patient can have >1 MACE

Admission, re-admission, ED revisits and diagnostic procedures

A total of 226 patients (35%) were admitted to the hospital after presentation at the ED, a total of 57 patients (9%) were re-admitted and 49 patients (8%) revisited the ED within 6 weeks. In total 246 exercise ECG tests were performed, 41 myocardial scintigraphies, 8 cardiac MRIs, 5 CCTAs, and 89 CAGs.

Within the low-risk TIMI group, 5 patients (5%) were admitted after ED presentation, compared to 28 patients (11%) in the low-risk HEART group. Furthermore, within 6 weeks 10 patients (10%) revisited the ED 11 times within the low-risk TIMI group and 22 patients (9%) from the low-risk HEART group revisited the ED 27 times. Within the low-risk TIMI group, 44 exercise ECG tests (42%), 2 myocardial scintigraphies (2%), 1 cardiac MRI (1%), 1 CCTA (1%), and no CAGs were administered. In the low-risk HEART group 106 bicycle stress tests (41%), 5 myocardial scintigraphies (2%), 4 cardiac MRIs (2%), 4 CCTAs (2%), and 7 CAGs (3%) were performed. Further information on use of health care resources is found in Table 5 and Table 6.

Costs

In total an estimated €763,468 was spent during the 6 weeks of follow-up on 640 patients, of which €544,287 (71%) on hospital admission and re-admission costs and €219,181 (29%) on diagnostic procedures (Table 7). This €544,287 consisted of admissions at initial ED visit by 226 patients being admitted for a total of 1,191 days. The total costs of diagnostic procedures consisted of costs for the bicycle stress tests (€36,654; 17%), myocardial scintigraphy (€29,725; 14%), cardiac MRI (€3,384; 2%), CCTA (€1,500; 1%), and CAG (€147,918; 67%). Concerning the costs in the low-risk population, in the low-risk HEART patients, a total of €33,945 was spent on diagnostic procedures and an additional €30,162 on admission during initial presentation, resulting in a total cost of €64,107 (8.4% of the mentioned total costs of €763,468). On the other hand, in the low-risk TIMI patients, a total of €8,729 was spent on diagnostic procedures and €5,941 on hospital admission, resulting in potential savings of €14,670 (1.9% of total costs).

Table 5. Admission, ED revisit, and re-admission rates compared for low TIMI scores and low HEART scores

	Patients (n)	Initial presentation			Re-admissions				ED revisits		
		admitted		days (sum)	patients		re-admissions (n)	days (sum)	patients		revisits (n)
Low risk TIMI=0	105	5	5%	13	1	1%	1	2	10	10%	11
Low risk HEART=0-3	256	28	11%	66	5	2%	8	41	22	9%	27
Total all patients	640	226	35%	1,191	57	9%	69	369	49	8%	58

Table 6. Comparison of diagnostic procedures within 6 weeks for low HEART scores and low TIMI scores

	Patients (n)	Diagnostic procedures									
		Stress bicycle test		Myocard scintigraphy		Coronary CT-angiography (CCTA)		Cardiac MRI		Coronary angiography	
Low risk TIMI=0	105	44	42%	2	2%	1	1%	1	1%	0	0%
Low risk HEART=0-3	256	106	41%	5	2%	4	2%	4	2%	7	3%
Total all patients	640	246	38%	41	6%	5	1%	8	1%	89	56%

Table 7. Overview of the total costs on initial hospital admission and diagnostic procedures for low HEART scores and low TIMI scores

	Costs of performed diagnostic procedures (€)						Costs of initial admission (€)	Total costs of diagnostic procedures and initial admission (€)
	Stress bicycle	Myocard scintigraphy	CCTA	Cardiac MRI	CAG	Total	Admission costs	
Low risk TIMI=0	6,556	1,450	300	423	0	8,729	5,941	14,670
Low risk HEART=0-3	15,794	3,625	1,200	1,692	11,634	33,945	30,162	63,657

DISCUSSION

This additional analysis on medical consumption in 640 chest pain patients shows that admission, re-admission and ED revisit rates increase with higher TIMI and HEART scores. Diagnostic procedure rates were similar between HEART and TIMI within low-, intermediate- and high-risk groups. Only the use of bicycle stress tests declined as TIMI and HEART increased whereas use of CAG increased with increasing scores. However, the HEART score with a score between 0 and 3 identifies more low-risk patients at the ED than the TIMI score with a score of 0.

In the current study, 40% of chest pain patients received a low HEART score of 0 to 3, with a cumulative incidence of MACE of 1.6%. It remains unsure whether diagnostic procedures with limited predictive values are going to detect this 1.6% population. In this specific group with a low pre-test probability, reduction of diagnostics could diminish patient burden and hospital costs. The same goes for the low-risk TIMI group, however in this group the reduction of diagnostics is limited as only 105 (16%) patients with TIMI 0 are considered low-risk. This is due to the conservative nature of the TIMI score, resulting in a MACE incidence of 0% in its low-risk group. When including TIMI scores of 1 into the low-risk group, the number of patients will increase, however, the occurrence of MACE will increase as well. It is to be debated what is an acceptable yet achievable missed event rate for chest pain patients in our current health care system with ED overcrowding[5].

Our findings are consistent with other studies in terms of demonstrated safety of the HEART score for risk-stratification and its possible use in determining further policy to reduce medical consumption, especially in low-risk patients[9,11,14,15,18,19,26]. However, literature discussing TIMI and its incidence of MACE shows some discrepancy with our results. The TIMI low-risk group in this study consisted of patients with TIMI 0 and had an incidence of MACE of 0% within 6 weeks of follow up. Several studies found that even with a TIMI score of 0, patients did experience a risk of MACE up to 2.4%[9,24].

Chest pain patients often receive multiple diagnostic tests, with a risk of iatrogenic damage and furthermore are prone to false-positive or false-negative results, especially the exercise ECG test. Especially low-risk patients are a group in which medical consumption could be reduced. In our study, a total of €33,945 could have been saved on diagnostic procedures alone and an additional €30,162 could have been saved if patients with a HEART score of 0 to 3 had been reassured and discharged early from the ED. The possible total cost reduction amounted to €64,107 (8.4% of the mentioned total costs of €763,468). If the TIMI score would have been used to stratify risk categories and the low-risk TIMI group be discharged

with reassurance, a total of €8,729 would have been saved in diagnostic procedures and another €5,941 in hospital admission costs, resulting in potential savings of €14,670 (1.9% of total costs). Extrapolating our results from two hospitals with a total of 2,102 beds to all hospitals in the Netherlands (with a total of 45,000 beds[17]), the implementation of the HEART score as a risk stratifying tool could result in savings of €1,372,414, which is more than a fourfold increase compared to the TIMI score, which could reduce costs in the Netherlands with €314,058.

When discharging patients based solely on a score to reduce redundant medical consumption, it remains the question whether the rate of missed MACE is acceptable. In this study, four patients in the low-risk HEART score group experienced MACE within 6 weeks. The first of these patients (HEART score 3) had already been scheduled for CABG prior to presentation. The other two patients with a HEART score of 3, as well as the one patient with HEART 2, were diagnosed immediately with ACS at the ED and received elective PCIs in a later stage, indicating mild severity of disease in these patients. These cases show that the HEART score should not be blindly followed, but rather be used as a risk stratification tool.

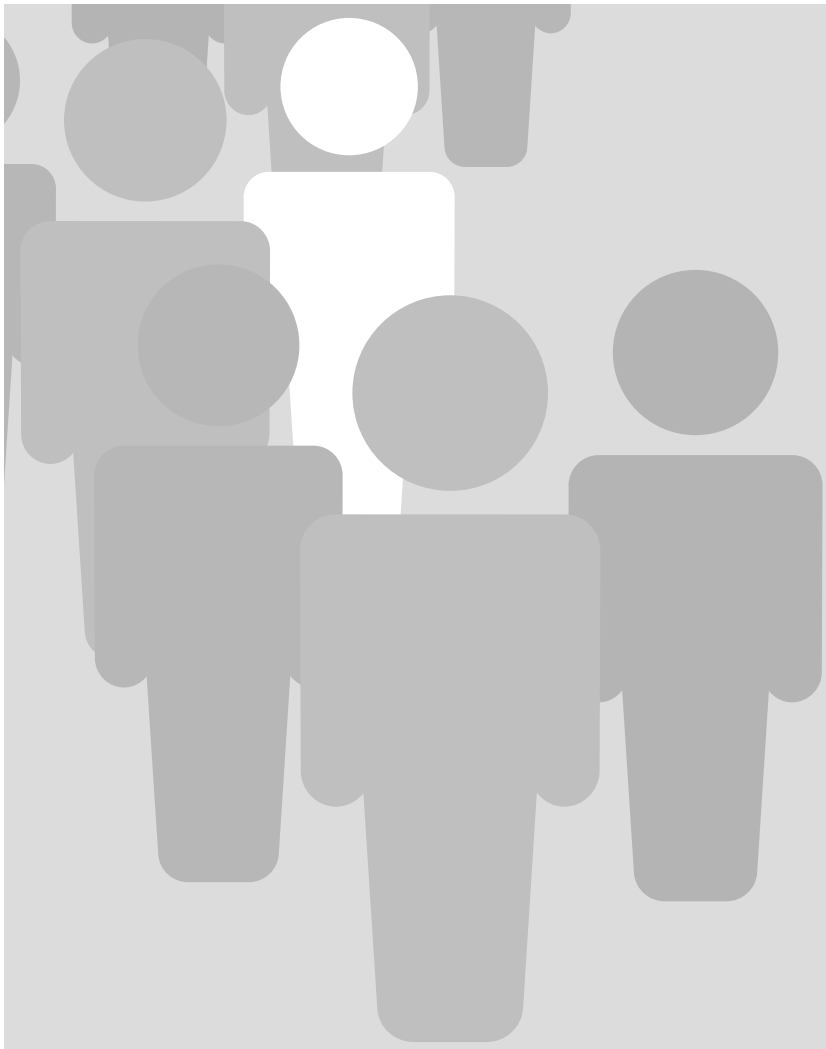
Our study may have several limitations. Firstly, any decisions on diagnostic testing and admissions were left to the clinicians. This should be taken into account when interpreting the results. However, because of the observational nature of our research question, this is surmountable. Secondly, since this is a sub analysis, a group of patients was selected from a larger sample, making estimation less definitive, especially in terms of safety. However, all patients who met the initial inclusion criteria were included in the original study, making selection bias less evident. Thirdly, we could have underestimated medical consumption because patients also received follow-up in other hospitals than where they had their initial presentation. However, we assume that most patients mention co-treatment in other hospitals to their physician at the ED, who reports this in the discharge letter, and thus was apparent to us. Lastly, a conventional troponin assay was used, since high-sensitive troponin was not yet introduced during the original study.

Our findings support previous studies that the HEART score aids medical decision-making in terms of risk stratification. The HEART score identifies more patients as low-risk compared to the TIMI score, which may lead to a reduction in diagnostic procedures and hospital admission in this low-risk group and thus in possible savings. Future studies should prospectively investigate whether adhering actively to the HEART score with an early discharge from the ED of low-risk patients, is indeed safe and leads to a reduction in the use of health care resources.

REFERENCES

1. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart 2005, 91 (2), 229-230.
2. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000, 342 (16), 1163-1170.
3. Hollander JE. Risk stratification of emergency department patients with chest pain: the need for standardized reporting guidelines. Ann Emerg Med 2004, 43 (1), 68-70.
4. Penumetsa SC, Mallidi J, Friderici JL, Hiser W, Rothberg MB. Outcomes of patients admitted for observation of chest pain. Arch Intern Med 2012, 172 (11), 873-877.
5. Brace-McDonnell SJ, Laing S. When is low-risk chest pain acceptable risk chest pain? Heart 2014, 100 (18), 1402-1403.
6. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2012, 60 (7), 645-681.
7. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2011, 32 (23), 2999-3054.
8. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 2000, 284 (7), 835-842.
9. Marcoon S, Chang AM, Lee B, Salhi R, Hollander JE. HEART score to further risk stratify patients with low TIMI scores. Cric Pathw Cardiol 2013, 12 (1), 1-5.
10. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al. Universal definition of myocardial infarction. Circulation 2007, 116 (22), 2634-2653.
11. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J 2008, 16 (6), 191-196.
12. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. Crit Pathw Cardiol 2010, 9 (3), 164-169.
13. Fesmire FM, Martin EJ, Cao Y, Heath GW. Improving risk stratification in patients with chest pain: the Erlanger HEARTS3 score. Am J Emerg Med 2012, 30 (9), 1829-1837.
14. Mahler SA, Miller CD, Hollander JE, Nagurney JT, Birkhahn R, Singer AJ, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. Int J Cardiol 2013, 168 (2), 795-802.
15. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol 2013, 168 (3), 2153-2158.
16. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. Crit Pathw Cardiol 2013, 12 (3), 121-126.
17. Six AJ, Backus BE, Kingma A, Kaandorp SI. Consumption of diagnostic procedures and other cardiology care in chest pain patients after presentation at the emergency department. Neth Heart J 2012, 20 (12), 499-504.
18. Leite L, Baptista R, Leitao J, Cochicho J, Breda F, Elvas L, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. BMC Cardiovasc Disord 2015, 15, 48.
19. Mahler SA, Hiestand BC, Goff DC, Hoekstra JW, Miller CD. Can the HEART score safely reduce stress testing and cardiac imaging in patients at low risk for major adverse cardiac events? Crit Pathw Cardiol 2011, 10 (3), 128-133.

20. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J 2005, 26 (9), 865-872.
21. Ramsay G, Podogrodzka M, McClure C, Fox KA. Risk prediction in patients presenting with suspected cardiac pain: the GRACE and TIMI risk scores versus clinical evaluation. QJM 2007, 100 (1), 11-18.
22. Yan AT, Yan RT, Tan M, Casanova A,; Labinaz M, Sridhar K, et al. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. Eur Heart J 2007, 28 (9), 1072-1078.
23. Backus BE, Six AJ, Kelder JH, Gibler WB, Moll FL, Doevendans PA. Risk scores for patients with chest pain: evaluation in the emergency department. Curr Cardiol Rev 2011, 7 (1), 2-8.
24. Pollack CV, Sites FD, Shofer FS, Sease KL, Hollander JE. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency department chest pain population. Acad Emerg Med 2006, 13 (1), 13-18.
25. Hakkaart-van Roijen L, Tan SS, Bouwmans CAM. Handleiding voor Kostenonderzoek; Instituut voor Medical Technology Assesment: Rotterdam the Netherlands, 2010.
26. Mahler SA, Riley RF, Hiestand BC, Russell GB, Hoekstra JW, Lefebvre CW, et al. The HEART pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. Circ Cardiovasc Qual Outcomes 2015, 8 (2), 195-203.
27. Mahler SA, Miller CD, Hollander JE, Nagurney JT, Birkhahn R, Singer AJ, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. Int J Cardiol. 2013;168(2):795-802.
28. Universitair Medisch Centrum Groningen. Tarieven Onderlinge Dienstverlening. https://www.umcg.nl/NL/Zorg/Professionals/tarieven_onderlinge_dienstverlening/Paginas/default.aspx (accessed Aug 17, 2015).



The impact of the HEART risk score in the early assessment of patients with acute chest pain: design of a stepped wedge, cluster randomised trial

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ABSTRACT

Background: Chest pain remains a diagnostic challenge: physicians do not want to miss an acute coronary syndrome (ACS), but, they also wish to avoid unnecessary additional diagnostic procedures. In approximately 75% of the patients presenting with chest pain at the emergency department (ED) there is no underlying cardiac cause. Therefore, diagnostic strategies focus on identifying patients in whom an ACS can be safely ruled out based on findings from history, physical examination and early cardiac marker measurement. The HEART score, a clinical prediction rule, was developed to provide clinicians with a simple, early and reliable predictor of cardiac risk. We set out to quantify the impact of the use of the HEART score in daily practice on patient outcomes and costs.

Methods: We designed a prospective, multicenter, stepped wedge, cluster randomised trial. Our aim is to include a total of 6600 unselected chest pain patients presenting at the ED in 10 Dutch hospitals during an 11-month period. All clusters (i.e. hospitals) start with a period of 'usual care' and are randomised in their timing when to switch to 'intervention care'. The latter involves the calculation of the HEART score in each patient to guide clinical decision; notably reassurance and discharge of patients with low scores and intensive monitoring and early intervention in patients with high HEART scores. Primary outcome is occurrence of major adverse cardiac events (MACE), including acute myocardial infarction, revascularisation or death within 6 weeks after presentation. Secondary outcomes include occurrence of MACE in low-risk patients, quality of life, use of health care resources and costs.

Discussion: Stepped wedge designs are increasingly used to evaluate the real-life effectiveness of non-pharmacological interventions because of the following potential advantages: (a) each hospital has both a usual care and an intervention period, therefore, outcomes can be compared within and across hospitals; (b) each hospital will have an intervention period which enhances participation in case of a promising intervention; (c) all hospitals generate data about potential implementation problems. This large impact trial will generate evidence whether the anticipated benefits of using the HEART score will indeed be achieved in real-life clinical practice.

Trial registration: ClinicalTrials.gov 80-82310-97-12154.

BACKGROUND

Patients presenting with chest pain at the emergency department (ED) pose a diagnostic challenge. Chest pain can be a symptom of an acute coronary syndrome (ACS), i.e. acute myocardial infarction (AMI) or unstable angina, which is the case in approximately 20% of the patients and requires prompt treatment. In the remaining 80%, chest pain is caused by many other, usually not life-threatening, conditions[1]. Unfortunately, decision-making in chest pain patients is hampered by limited predictive power of patient characteristics, including signs, symptoms and additional tests[1-3]. Therefore, physicians face the challenge of not wanting to miss an ACS on the one hand, while avoiding too many unnecessary diagnostic procedures that can be time-consuming and patient burdening on the other hand. Currently, the fear of missing a relevant cardiac condition makes physicians cautious and, to be on the safe side, a large proportion of patients are kept in the hospital from several hours to days for monitoring or additional testing.

Diagnostic strategies in patients with chest pain therefore focus on identifying patients in whom ACS can be safely ruled out based on readily available clinical findings from history, physical examination and early marker measurement of cardiac damage. Recent guidelines suggest the use of well-developed and validated risk scores to stratify patients in the emergency room[4-6]. Several prognostic risk scores have been developed for patients diagnosed *with ACS*, such as the TIMI (Thrombolysis in Myocardial Infarction) risk score and the GRACE (Global Registry of Acute Cardiac Events) risk score[7-9]. However, scores that *identify ACS* in patients suspected of ACS in the emergency setting and predict short-term mortality or coronary intervention are not available. The HEART score has been specifically developed for risk stratification in all patients with chest pain presenting at the ED.

The HEART score incorporates all five important elements of clinical judgement in chest pain patients: History, ECG (electrocardiogram), Age, Risk factors and Troponin (see Table 1). Similar to the Apgar score, applied worldwide to assess the need for intensive care in newborns[10], each of the five elements is appreciated with 0, 1 or 2 points. The sum of all five elements results in a score between 0–10, which can easily be calculated. The HEART score has been externally validated in various patient populations with a total of 6174 patients and its predictive effectiveness has been demonstrated[11-14]. Table 2 depicts an overview of these validation studies. In the Dutch multicenter validation study, major adverse cardiac events (MACE) occurred in 1.7% (95% CI 1.2-2.2) of all patients with a HEART score of 3 or lower. This is comparable with the around 2% incidence of ACS among discharged chest pain patients reported in the literature[15,16]. Importantly, none of the patients in the low-risk HEART category experienced unexpected sudden cardiac death in our validation studies.

MACE occurred in 16.6% of all patients with intermediate HEART scores (4–6), and in 50.1% of all patients with high HEART scores (7–10). Similar results were observed in relevant patient subgroups, such as women, elderly or diabetics[12]. Notwithstanding these promising validation results, the impact of the use of the HEART score in daily clinical practice remains to be established. The HEART score provides the physician with a formal risk score and a recommendation whether a chest pain patient should be admitted or not. A safe and early discharge could potentially result in a significant reduction of patient burden, hospital admissions and health care costs. Therefore, we designed the HEART Impact study to investigate whether the use of the HEART score in the management of chest pain patients indeed leads to these positive health effects, while not causing an increase in the occurrence of MACE.

Table 1. Elements to calculate HEART score for chest pain patients at the emergency department

History	Highly suspicious	2
	Moderately suspicious	1
	Slightly or non-suspicious	0
ECG	Significant ST-depression	2
	Nonspecific repolarization disturbance	1
	Normal	0
Age	≥ 65 years	2
	>45 – <65 years	1
	≤ 45 years	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 **Range: 0-10**		

*Risk factors include: currently treated diabetes mellitus, current or recent smoker, diagnosed and/or treated hypertension, diagnosed hypercholesterolemia, family history of coronary artery disease (CAD), obesity (body mass index (BMI) >30)
^History of atherosclerotic disease include: coronary revascularization, myocardial infarction, stroke, or peripheral arterial disease, irrespective of the risk factors for CAD

Table 2. Summary of results of previous validation studies of the HEART score

				Total
Number of patients	N = 880[12]	N = 2,388[13]	N = 2,906[14]	N = 6,174
Design	Retrospective	Prospective	Prospective	
Countries	The Netherlands	The Netherlands	9 countries in the Asia-Pacific region	
Participating hospitals	4	10	14	
Inclusion period	Jan '06 – Mar '06	Oct '08 –Nov '09	Nov '07 – Dec '10	
Type of patients	Patients presenting with chest pain at the ED	Patients presenting with chest pain at the ED	Patients presenting with chest pain at the ED	
MACE definition	AMI, revascularisation, all cause death	AMI, revascularisation, stenosis managed conservatively, all cause death	AMI, revascularisation, death unless clearly non-cardiac	
Duration of follow-up	6 weeks	6 weeks	4 weeks	
Cumulative incidence of MACE stratified by HEART scores				
0-3	0.99%	1.7%	1.7%	1.6% (95%-CI 1.1-2.2)
4-6	11.6%	16.6%	14.3%	12.5% (95%-CI 11.3-13.7)
7-10	65.2%	50.1%	50.0%	49.4% (95%-CI 46.4- 52.4)

ED: emergency department, AMI: acute myocardial infarction, MACE: major adverse cardiac event, 95%-CI: 95%- confidence intervals

METHODS

Study design: stepped wedge randomised trial

We will use a prospective, stepped wedge cluster randomised trial[17,18]. Our aim is to include 6600 unselected chest pain patients from 10 hospitals in the Netherlands during an 11-month period. Key study design features are shown in Figure 1 and Figure 2. In a stepped wedge design, there is no randomisation at patient level, but hospitals will be randomised with respect to the timing at which they introduce the HEART score. See Figure 1. During the first month, all chest pain patients presenting to the ten hospitals will receive usual care. Then, during a 10-month period, each month one randomly allocated hospital will start to apply the HEART score (HEART care period) and continue to do so until the end of the study. During the last month of the inclusion period all 10 hospitals will be using the HEART score.

Figure 1. The stepped wedge design for the HEART Impact study

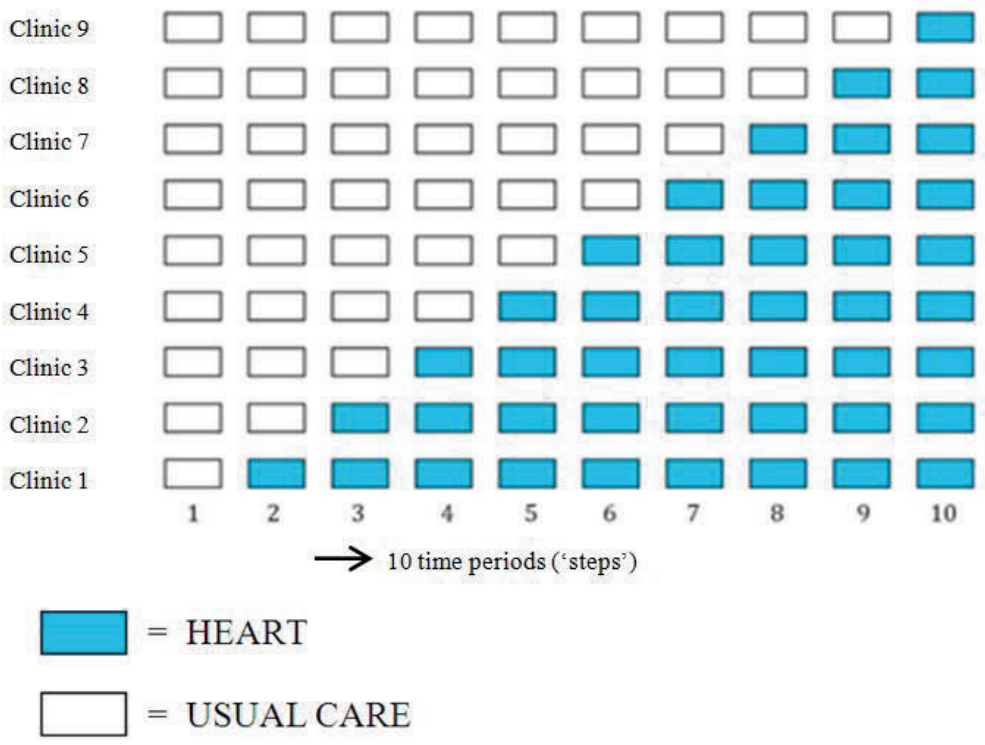
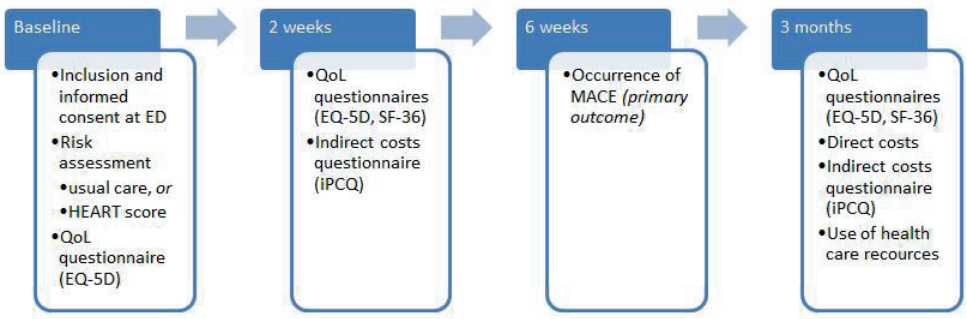


Figure 2. Flow of study and data collection in usual care period and in HEART care period



ED: emergency department, QoL: quality of life, EQ-5D: EuroQol Five-Dimensional, SF-36: short-form 36, iPCQ: productivity cost questionnaire, MACE: major adverse cardiac events

'Usual care' and 'HEART care' period

Usual care is defined as 'daily practice of the cardiologist or attending emergency physician to diagnose a patient with chest pain'. In this period, attending physician assess the risk based on their clinical skills, previous experiences, gut feeling and various other criteria (for example, described in European Society of Cardiology Guidelines[6]), without using the HEART score. No attempt was made to explicitly standardise usual care across all hospitals. The assessment will typically include: gender, age, medical (cardiac) history, symptoms, risk factors, and current drug use, physical examination with special attention for the heart and lungs, blood pressure, heart rate, blood tests, ECG, and any other diagnostic procedures the physician considers necessary. The standard blood tests include measurements of troponin, glucose levels, creatinin levels (with a calculated estimated glomerular filtration rate (eGFR) according to MDRD (modification of diet in renal disease)), haemoglobin, and any other blood test required. A standard 12-lead ECG is recorded by a trained employee of the ED and classified by a single cardiologist according to the Minnesota coding criteria. All investigations take place in the ED.

During the HEART care period, the HEART score will be formally determined in all patients. Decision-making about whether to admit a patient, any further testing or treatment decisions will be carried out similarly to usual care, with the exception of the availability of the HEART score in each individual patient and the recommendations linked to that score. This is also known as "directive use" of a prediction rule, as opposed to "assistive use" where only the predicted risk is given to the physician[19]. The recommendation for patients with a HEART score of 3 or lower will be reassurance and discharge. In those low-risk patients who are discharged, a second troponin will be performed at home to identify any missed ACS. A similar approach of home visits performed by ambulatory lab services was successfully applied in our earlier study in suspected ACS in primary care[20]. Obviously, in accordance

with daily practice, the attending physician may decide to overrule the recommendation corresponding to a low HEART score and admit a patient. In such a case, information about the reasoning for this escape will be collected. Patients with a HEART score in the intermediate range (4–6), will generally be admitted to the hospital for further observation and investigation. The high-risk group (7–10) will typically receive prompt (invasive) treatments.

Study population and recruitment

All patients above 18 years presenting with chest pain to the (cardiac) ED of 10 participating hospitals are eligible. Only patients presenting with evident ST-segment elevation myocardial infarction (STEMI) will be excluded, since there is no diagnostic dilemma in these patients. Typically, such patients are directly taken to the intervention room. In both study periods, information about the study procedure will be provided by the treating physician and written consent for the use of data and follow-up is obtained at the first appropriate moment after presentation at the ED. In the HEART care period, no consent from the patient is needed for the use of the HEART score, for several reasons. First, the number of additional procedures for patients is minimal since the HEART score consists of elements that are collected routinely. Furthermore, the HEART score is proven to be safe, and is a decision support tool rather than a real intervention, with the possibility for physicians to override the recommendations provided by the rule. The study was approved by the Institutional Review Board, and subsequently by the Boards of the participating hospitals.

Outcome measures

The HEART impact trial aims to measure both the intended positive changes as well as any unintended negative effects associated with the use of the HEART score. Patient outcomes, use of health care resources and costs will be determined in both periods.

Primary outcome: occurrence of MACE

The primary outcome is the 6-week occurrence of major adverse cardiac events (MACE), consisting of the following events: acute myocardial infarction (AMI), Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG) surgery, or death due to any cause. To identify MACE after discharge, a phone-call will be made to all patients at home after 3 months. Any information that could indicate to possible endpoints will be further investigated through hospital charts, hospital discharge letters and information obtained from the patient's general practitioner (GP). In addition, the Central Bureau for Statistics (CBS) will be consulted for information on vital status as the cause of death of participants. All cases with possible endpoints are reviewed by two independent adjudicators for endpoint classification. This adjudication committee will evaluate all relevant information

to decide, using ESC guidelines, whether MACE occurred. In case of disagreement between two adjudicators, the case is discussed in a plenary adjudication committee meeting until consensus is reached.

Secondary outcomes include the following:

- The occurrence of MACE in the specific subgroup of patients with a low HEART score.
- Use of health care resources. The number of hospital admissions/discharges, duration of hospital stay, duration of stay on the ED, number of readmissions and GP visits after discharge will be collected.
- Health-related quality of life. This will be determined in a subset of approximately 1000 patients, in both time periods in five of the participating hospitals. Data on health-related quality of life are collected at baseline (at ED) using the EuroQol Five-Dimensional (EQ-5D) questionnaire, and a 2-week and at 3-month follow-up using the short form-36 (SF-36) and the EQ-5D questionnaires. SF-36 is a short-form health survey with only 36 questions. For this study, we will only use the 11 questions addressing Health. EQ-5D comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Furthermore, the EQ VAS (visual analogue scale) records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. Higher scores are associated with a better health-related quality of life.
- Direct and indirect costs. These will be determined in a subset of approximately 1000 patients, in both time periods in five of the participating hospitals. Actual medical costs using a health-care provider's perspective are obtained in both the time periods. Medical resource use is extracted from the electronic hospital patient files. Unit cost prices will be determined in two participating hospitals, one academic and one peripheral hospital, using micro-costing if possible and top down costing otherwise. The iPCQ (Productivity Cost Questionnaire) will be used to collect quantitative data on the relation between illness, treatment and work performance. The iPCQ is divided into 3 modules: (1) reduced productivity at paid work due to work absenteeism, (2) reduced productivity at paid work without absence from work and (3) unpaid labour production.

Statistical analyses

The 6-week cumulative incidence of MACE in both the intervention and usual care period will be analysed at the patient level using a generalised linear mixed model (GLMM)[21]. Risk differences with corresponding 95% CIs will be estimated from this model. No baseline differences in prognostic factors between patients included in both periods are expected, but in case these do occur, covariates will be added to the GLMM model to adjust for these baseline differences. Differences in health-related quality of life at baseline, 2 weeks and

at 3 months will also be assessed, separately for the different questionnaires. Costs per patient will be calculated according to Dutch guidelines for pharmaco-economic analyses[22], and costs of drugs prescribed will be based on Dutch formulary cost-prices.

Sample size

The aim of the HEART study is to evaluate whether the use of the HEART score streamlines the further management of chest pain patients, in particular whether it can identify low-risk patients who can be discharged sooner than usual. However, these benefits become only relevant if the use of the HEART score does not lead to an increase in adverse cardiac events. Our sample size calculation is therefore based on demonstrating that proportion of patients with MACE is not inferior to the proportion observed with usual care. The proportion MACE expected during usual care is 17%. The non-inferiority margin is based on clinical judgement and available literature as 3%, thus accepting an upper limit of the 95% confidence interval (CI) during the intervention period of 20%. With 10 hospitals, inclusion of 60 patients per hospital per month, a between-hospital variation in incidence of 16 to 18%, a one-sided alpha of 5% and a power of 80%, 6600 patients with chest pain should be included in total. Taken into account our inclusion rates of previous validation studies and with special attention and encouragement for inclusion, we expect a realistic inclusion rate of 60 patients per hospital per month.

Cost-effectiveness analysis

A cost-effectiveness analysis will be performed from a societal perspective, for a 3-month and a life-time time horizon. The 3-month time horizon corresponds to the actual follow-up period and will consider the observed differences in costs and quality of life. A GLMM will be used to assess cost-effectiveness, accounting for the randomisation of clusters instead of patients. Uncertainty will be addressed through the GLMM model which will be extended with cluster and patient-level covariates if baseline characteristics are imbalanced. The life-time horizon will be applied to account for long-term costs and effects of the observed MACE. Here, the observed risks of MACE, as well as the direct treatment cost and productivity losses estimated using the friction cost approach, will serve as input for a Markov decision-analytic model[23]. If necessary, additional evidence on long-term costs and effects of adverse events will be obtained from the literature. Monte Carlo simulation will be applied to simulate the course of hypothetical patients through the model, and to estimate the number of quality-adjusted life years and costs of both strategies. Costs will be discounted with 4% per annum, and effects with 1.5% per annum, according to Dutch guidelines. The incremental cost-effectiveness ratio and the net monetary benefit (for various willingness to pay thresholds) will be estimated for the HEART score compared with usual care. Uncertainty will be assessed with probabilistic sensitivity analysis[24], and results will be presented in incremental cost-effectiveness planes and cost-effectiveness acceptability curves.

Regulation statement

This study will be conducted according to the principles of the current version of the declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO).

Ethics committee approval

The study was approved by the Institutional Review Board (medical ethical committee of the University Medical Center Utrecht, the Netherlands), and subsequently by the Boards of the participating hospitals.

DISCUSSION

Clinical prediction rules, like any other health care intervention, need proper evaluation before wide-spread use in clinical practice. Two key steps in this evaluation include external validation and impact assessment. External validation studies can reveal several problematic issues associated with the use of a clinical prediction rule[25-27]. Firstly, the rule has been developed on a dataset that was too small in relation to the number of variables that have been considered. This increases the risk that particularities of the dataset will be modeled rather than robust relationships. The consequence is that the performance of the model will decrease when applied to new patients (external validation). This is known as over-fitting. Secondly, the rule has been derived in a population which does not match the population where clinicians would like to use the rule. Here, your prediction model may be developed statistically sound, but applied to a new population the performance may decrease meaningfully. However, even after proper development and good performance in validation studies, often clinical prediction rules are hardly or incorrectly used in daily practice, because of difficulties in application or because physicians are not convinced of its usefulness in clinical practice. This is especially the case when the outcome used in the rule has no direct relevance for clinical practice. For all these reasons, it is of vital importance to study the impact of a clinical prediction rule when applied in real-life practice. Increasingly, stepped wedge designs are applied to measure the impact of clinical decision rules in clinical practice[28].The stepped wedge design combines elements of both the cluster randomised trial and the before-after design (see Figure 1). The stepped wedge design has several features that make this design attractive for such impact studies. These characteristics are outlined in Table 3. We chose the stepped wedge design as an informative, efficient and valid design to examine whether expected improvements in patient outcomes, use of health care resources, and costs can be achieved when implementing a health care intervention on a large scale.

Table 3. Overview of key characteristics of the stepped wedge design

(i)	Stepped wedge design has features of cluster randomisation, i.e. during a specific time period only type of intervention (usual care or HEART score) is administered
	a. this reduces the risk of contamination
	b. the effect of clustering needs to be taken into account in the statistical analysis
(ii)	Stepped wedge design has features of a one direction cross-over trial, i.e. each hospital contributes data from both usual care and HEART score in a fixed order.
	a. allows for comparison of results within hospitals which may be less confounded by differences in case mix than between hospitals
	b. the fixed order from usual care to HEART score further reduces the risk of contamination as the HEART score is relatively simple to calculate.
	c. due to the cross-over, each hospital will provide data about the (problems in) implementation of the HEART score
(iii)	Switch from usual care to HEART score in hospitals is evenly and randomly distributed over calendar time
	a. this reduces the impact of potential changes over time in other factors than the intervention
	b. it facilitates the close monitoring and logistic of all activities surrounding the switch
(iv)	Gradual implementation of new strategy is carried out, thereby providing data about the process itself.

CONCLUSION

It is of importance to generate valid evidence that the use of the HEART score compared to usual care is safe and leads to fewer admissions and diagnostic procedures in real-life clinical practice. Using the stepped wedge design, we can also monitor the process of implementation of a clinical support tool at the ED across hospitals that vary in size and population. Patient inclusion has started July 1st of 2013.

ACKNOWLEDGEMENTS

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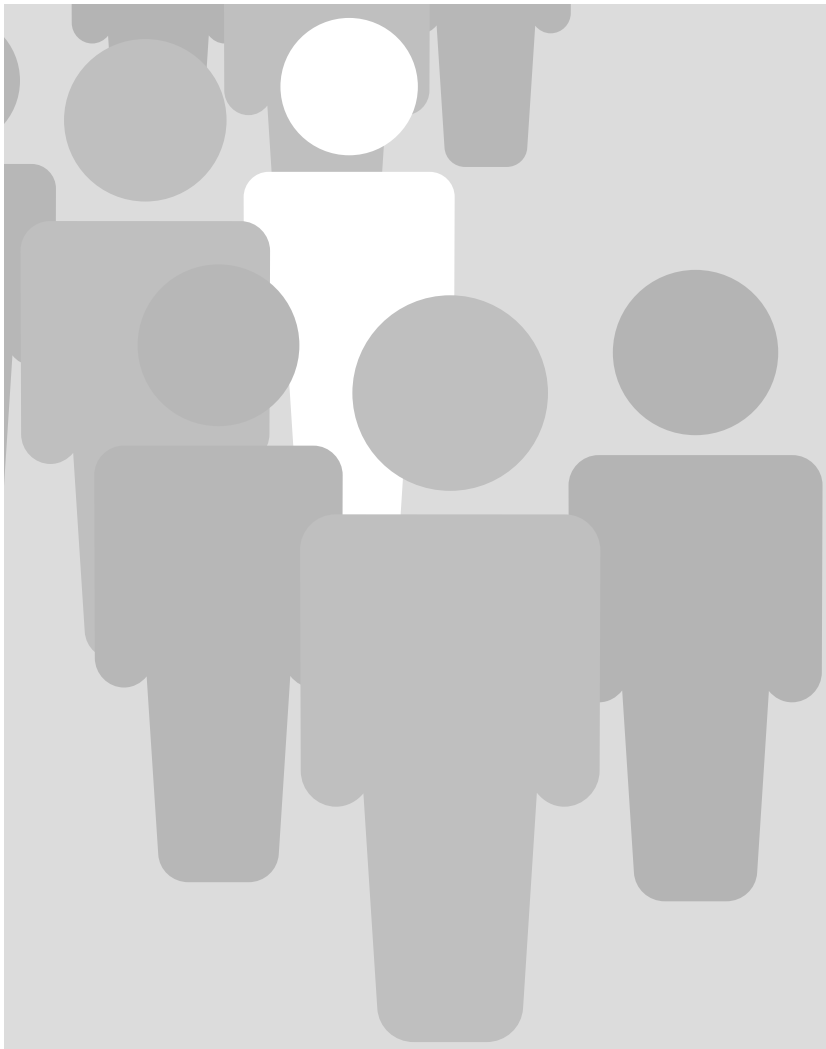
REFERENCES

1. Lee TH, Goldman L. Evaluation of the patient with acute chest pain. N Engl J Med 2000, 342:1187–1195.
2. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. JAMA 2005, 294:2623–2629.
3. Miller CD, Lindsell CJ, Khandelwal S, Chandra A, Pollack CV, Tiffany BR, et al. Is the initial diagnostic impression of "noncardiac chest pain" adequate to exclude cardiac disease? Ann Emerg Med 2004, 44:565–574.
4. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2009, 338:b606.
5. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction. J Am Coll Cardiol 2007, 50:e1–157.
6. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2011, 32(23):2999–3054.
7. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ 2006, 333:1091.
8. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/ non-ST elevation MI. JAMA 2000, 284:835–842.
9. de Araújo GP, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J 2005, 26:865–872.
10. Apgar V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg 1953, 32(4):260–7.
11. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J 2008, 16:191–6.
12. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room; a multicenter validation of the HEART score. Crit Path Cardiology 2010, 9:164–169.
13. Backus BE, Six AJ, Kelder JC, Bosschaert MAR, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol 2013:S0167–5273.
14. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. Crit Path Car 2013;12: 121–126.
15. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000, 342:1163–1170.
16. Schull MJ, Vermeulen MJ, Stukel TA. The risk of missed diagnosis of acute myocardial infarction associated with emergency department volume. Ann Emerg Med 2006, 48:647–55.
17. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC Med Res Methodol 2006, 6:54.
18. Brown C, Hofer T, Johal A, Thomson R, Nicholl J, Franklin BD, et al. An epistemology of patient safety research: a framework for study design and interpretation: part 2. study design. Qual Saf Health Care 2008, 17:163.
19. Moons KG, Kengne AP, Grobbee DE, Royston P, Vergouwe Y, Altman DG, et al. Risk prediction models: II: external validation, model updating, and impact assessment. Heart 2012, 98(9):691–8.
20. Bruins Slot MH, van der Heijden GJ, Rutten FH, van der Spoel OP, Mast EG, Bredero AC, et al. Heart-type fatty acid-binding protein in acute myocardial infarction evaluation (FAME): background and design of a diagnostic study in primary care. BMC Cardiovasc Disord 2008, 8:8.

21. Molenberghs G, Verbeke G. Models for discrete longitudinal data. Springer, New York; 2005.
22. Richtlijnen voor farmaco-economisch onderzoek – geactualiseerde versie 2006 [Guidelines for pharmaco-economic research]. Diemen: College voor Zorgverzekeringen (CvZ) [Health Insurance Board]; 2006.
23. Oostenbrink JB, Bouwmans CAM, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg - geactualiseerde versie 2004. Diemen: College voor Zorgverzekeringen (CvZ) [Health Insurance Board]; 2004.
24. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000, 17:479–500.
25. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. Ann Intern Med 2006, 144:201e9.
26. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996, 15:361e87.
27. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. Ann Intern Med 1999, 130:515e24.
28. Mdege ND, Man MS, Taylor Nee Brown CA, Torgerson DJ. Systematic review of stepped wedge cluster randomized trials shows that design is particularly used to evaluate interventions during routine implementation. J Clin Epidemiol 2011, 64(9):936–48.



Impact of using the HEART score in chest pain patients at the emergency department: a stepped wedge, cluster randomized trial

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Submitted

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ABSTRACT

Background: The HEART score is a simple instrument to stratify chest pain patients according to their probability of acute coronary syndrome, but its impact in daily practice is not known. We designed the HEART-Impact trial to measure the impact of its use on clinical outcomes and use of health care resources.

Methods: In a stepped wedge, cluster randomized trial, we included chest pain patients presenting at emergency departments (ED) in 9 Dutch hospitals between 2013 and 2014. All hospitals started with a 'usual care' period and over time hospitals consecutively switched to 'HEART care' in a randomly assigned order. During HEART care, the score was calculated by the treating physician for each patient with corresponding management recommendations for admission or discharge. For safety, a non-inferiority margin was set at an absolute increase in the 6-week incidence of major adverse cardiac events (MACE) of 3% during HEART care. Main other outcomes included use of health care resources, quality of life, and cost effectiveness.

Results: In total 3,648 patients were included, 1,827 receiving usual care and 1,821 HEART care. Six-week incidence of MACE during HEART care was 1.3% lower than during usual care (upper limit 95% CI: +2.0%). In low-risk patients (HEART score ≤3), MACE occurred in 2.0% (95% CI: 1.2-3.3) of the patients. The proportion of early discharge within 4 hours after initial presentation was higher during HEART care (34.4 vs. 30.6%, difference after adjustment for clustering and time steps 0.7%; 95% CI: -10.6 to +11.9%). No difference in readmissions, recurrent ED visits or GP visits occurred, but out-patient clinic visits increased, although not statistically significant.

Conclusion: The use of the HEART score during initial assessment of chest pain patients is safe but the impact on the use of health care resources was limited, probably due to hesitations to base patient management on the score.

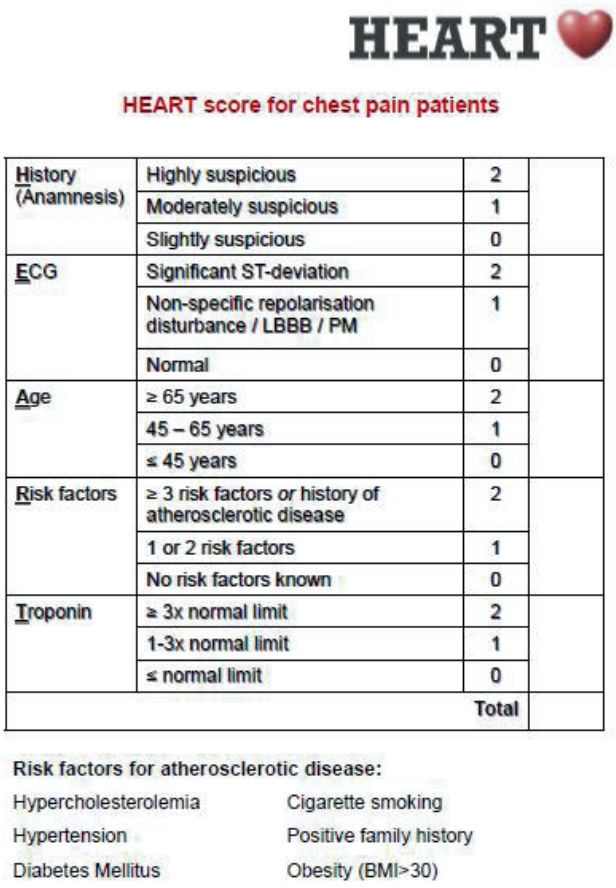
Trial registration: ClinicalTrials.gov 80-82310-97-12154.

BACKGROUND

Patients presenting with chest pain account for 6% of all emergency department (ED) visits[1], corresponding with 8 million visits to EDs in the US each year[2,3]. In around 20% of these patients, the chest pain is caused by an acute coronary syndrome (ACS) and requires prompt admission and treatment. However, in the remaining 80%, the underlying condition is non-cardiac and mostly not life-threatening[4]: these patients could be discharged from the ED, and managed further by a general practitioner (GP) or at the out-patient clinic. The diagnosis of ACS can be challenging. Approximately 50% of the patients do not have classical symptoms of ACS[5], and coronary angiography (CA) as the reference standard of investigation is invasive, costly and carries the risk of complications. Current management in the Netherlands as well as worldwide is rather conservative, with two thirds of patients being admitted or monitored at the ED, and often receiving unnecessary additional testing, which puts a large burden on health care resources[1]. Despite the current, conservative management, around 2% up to 6% of patients with ACS are still being missed[6,7].

International guidelines advise the use of risk stratifying instruments in chest pain patients, as these are superior to clinical assessment alone[8]. However, the impact on patient outcomes of the use of these instruments has not been investigated[8]. Over the years several instruments have been developed, such as the TIMI score, the GRACE score and the HEART score, the latter being specifically developed for chest pain patients[9]. The HEART score is based on five key elements in the initial work-up of patients with chest pain: History, ECG, Age, Risk factors and Troponin (see Figure 1). Each of the five elements is scored as 0, 1 or 2 points, leading to a maximum score of 10. Calculation of the HEART score provides the physician with a formal recommendation for admission, observation or discharge in individual patients. The HEART score showed promising results in external validation studies in various countries and types of hospitals[10-17]. We determined whether the use of the HEART score reduced patient burden, hospital admissions and health care costs, while not leading to an increase in the occurrence of adverse cardiac events.

Figure 1. HEART score for chest pain patients

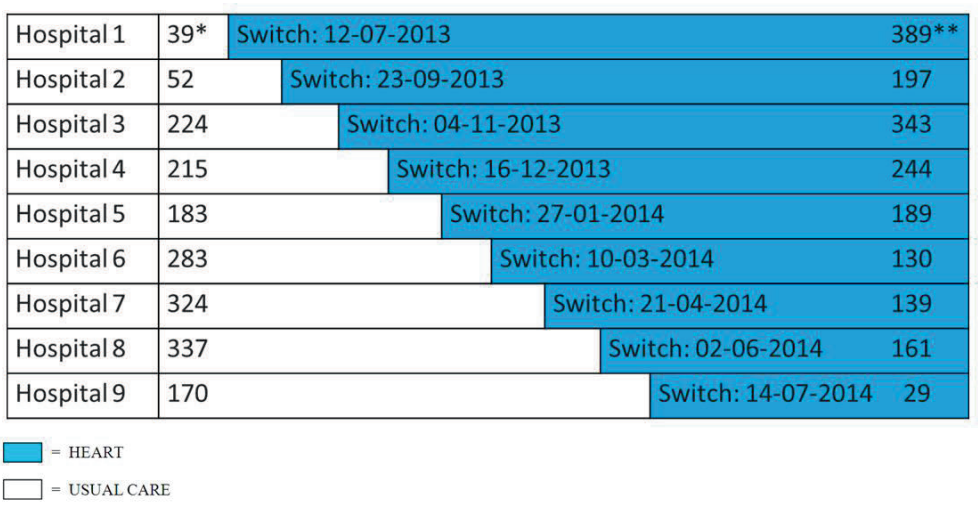


METHODS

Study design

The design of our trial has been previously described in detail[18]. We conducted a prospective, stepped wedge cluster randomized trial, see Figure 2[19]. In this stepped wedge design all hospitals (clusters) started with an initial period of usual care. Subsequently, at regular intervals ("steps") each hospital switched to "HEART care", i.e. the use of the HEART score. At the end of the trial all hospitals had crossed over to using the HEART score. The order in which hospitals switch is randomized. A total of nine hospitals in the Netherlands participated. In none of these hospitals the HEART score was implemented or used before start of the trial. Characteristics of participating hospitals and the used troponin assays are shown in Appendix 1 and Appendix 2.

Figure 2. Stepped wedge design in the participating hospitals for the HEART-Impact trial



Inclusion period: 1st of July 2013 – 31st of August 2014
* inclusion numbers in usual care period
** inclusion numbers in HEART care period

Study population

All chest pain patients above 18 years presenting with chest pain to the (cardiac) ED of nine participating hospitals were eligible. Exclusion criteria were evident ST-segment elevation myocardial infarction (STEMI), language barriers, unable or unwilling to give informed consent. Patients were informed on the aim of the study by the treating physician and written consent for the use of data and follow-up was obtained. The study was conducted according to the principles of the current version of the declaration of Helsinki and in accordance with the Dutch law on Medical Research Involving Human Subjects Act (WMO). The trial was approved by the Institutional Review Board of the University Medical Center Utrecht, the Netherlands, and subsequently by the Boards of the participating hospitals.

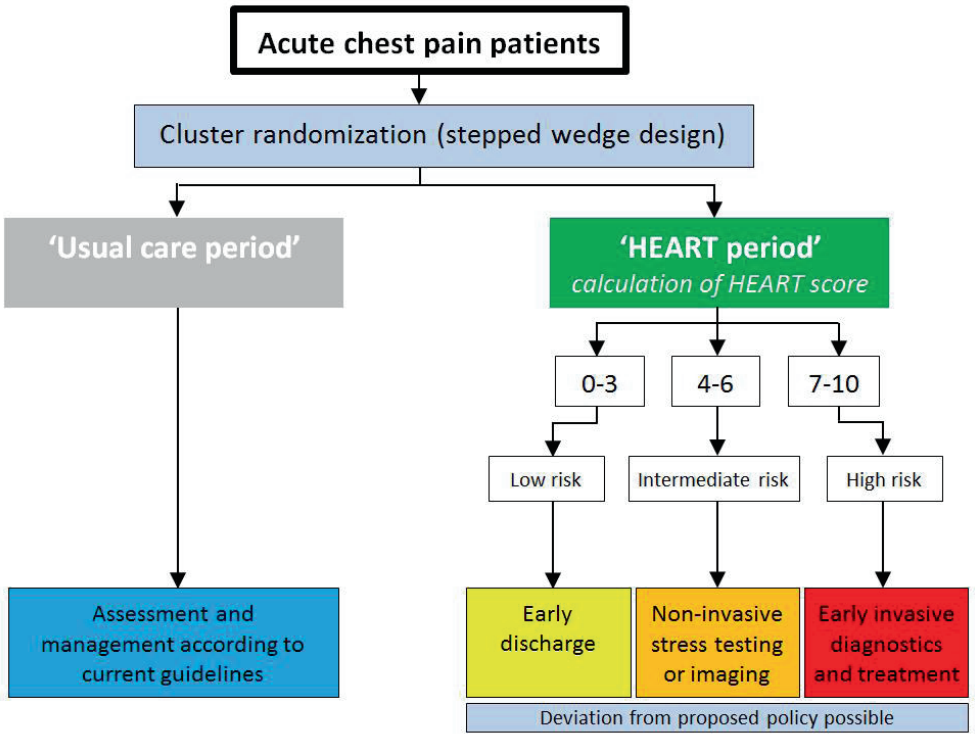
***'*Usual care' versus 'HEART care' (Figure 3)**

"Usual care" was defined as 'daily practice of the cardiologist or attending emergency physician to evaluate a patient with chest pain'. In this period, attending physicians assessed the risk at the ED based on their clinical expertise, previous experiences, gut feeling and (inter)national clinical guidelines[8], without the calculation and use of the HEART score.

"HEART care" consisted of routine initial work-up with additionally the HEART score being formally determined in all patients and then linked to specific recommendations for further management (so called directive use[20]). The recommendation for patients with a HEART

score of 3 or lower was reassurance and discharge, without further diagnostic testing. In those low-risk patients who were discharged without a representative troponin, a second troponin was performed the same or next day at home to identify any missed ACS. If this approach was logistically not feasible, a second troponin was performed during their stay at the ED. Recommendations for patients with a HEART score in the intermediate-risk group (4-6) and for the high-risk group (score 7-10) were admission to the hospital for further observation and investigation, and prompt (invasive) treatments, respectively. In accordance with daily practice, the attending physician could decide to overrule the recommendation corresponding to the HEART score and for example admit a patient with a low score. In such cases, information about the reasons for not following the recommendation was collected. We prepared our participating hospitals before the start of inclusion with presentations during morning meetings, and personal instruction of the residents, nurses and cardiologists. Residents, nurses and cardiologists were informed about the timing of the switch to HEART care, just one week before the actual switch, with a meeting reviewing patient cases and exercises on calculation of the HEART score.

Figure 3. Study protocol of the HEART-Impact trial



Outcome measures

Primary outcome

The primary outcome was the "safety" outcome: i.e. the 6-week occurrence of major adverse cardiac events (MACE), consisting of the following events: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), unstable angina (UA), percutaneous coronary intervention (PCI), coronary arterial bypass grafting (CABG), or death due to any cause. All these endpoints were defined according to recent guidelines[8,21]. To identify MACE after discharge, all patients were contacted by phone at home after 3 months. If we were not successful after multiple attempts, contact by e-mail was sought or the patient's GP was contacted. Any information indicative of a relevant endpoint or use of health care resources was further investigated through consulting electronic hospital medical files and hospital discharge letters. All episodes indicating to a potential safety endpoint were reviewed by two independent cardiologists for final classification. These adjudicators evaluated all relevant information to decide whether MACE occurred or not, based on the definitions included in the relevant ESC (European Society of Cardiology) guidelines. In case of disagreement between two adjudicators, the case was discussed in a consensus meeting with at least three cardiologists being present.

Use of health care resources

The number and causes of initial admissions, readmissions, recurrent ED visits, out-patient clinic visits within three months after the initial presentation were recorded in all patients. The number and reason of GP visits were asked during the telephone call with the patient. It was decided in advance to collect detailed data on the use of different cardiac diagnostic and therapeutic procedures in five of the nine participating hospitals.

Quality of life

Quality of life data were collected in patients from the same five participating hospitals during both usual and HEART care, at baseline, and at 2-week and at 3-month follow-up using the EuroQol Five-Dimensional (EQ-5D) questionnaire[18].

Direct costs

Health care resource use was extracted from the electronic hospital patient files from the same five participating hospitals. Unit cost prices were determined using the available literature[22].

Statistical analyses

The 6-week cumulative incidence of MACE was analyzed using generalized linear models (GLM). The generalized estimating equation (GEE) approach was applied to take clustering of outcomes within hospitals into account[19,23]. Risk differences with corresponding 95% confidence intervals (CI) were estimated in order to evaluate non-inferiority of the main safety outcome of MACE. To directly estimate risk differences we used the identity link and the binomial distribution within the GLM. Our main model included type of care (usual care and HEART care) and steps (time) as a categorical variable. In subsequent models we adjusted for the following prognostic factors that could act as confounders: age, gender, any cardiovascular history and risk factors for CVD. We pre-specified three relevant subgroups to investigate whether the effect of HEART with respect to the incidence of MACE differed in men vs. women, above vs. below 75 years of age, diabetics vs. non-diabetics. A formal test of interaction was performed by adding the subgroup-by-treatment interaction to the model. The same modelling approach was applied for other binary outcomes: proportion of patients with early discharge; discharged from ED, readmitted; out-patient clinic visits; ED revisits; and diagnostic tests.

Sample size

The sample size calculation was based on demonstrating that the use of the HEART score would not lead to an absolute increase in the incidence of MACE of more than 3%. This non-inferiority margin was based on clinical judgement and available literature. Therefore, the 95% one-sided upper limit of the CI of the difference in MACE between HEART and usual care should not exceed 3%. The proportion MACE expected during usual care was 17%, and correlation in outcomes within hospitals was estimated at 16 to 18%. Based on these numbers, and a stepped wedge design with 10 clusters, the total sample size was calculated at 6,600[18].

Cost-effectiveness analysis

Differences in health-related quality of life at baseline, 2 weeks and at 3 months were assessed for the EQ-5D questionnaire. Costs per patient were calculated according to Dutch guidelines for pharmaco-economic analyses[22]. Bootstrapping (n=2,500) was used to obtain 95% CIs around differences in quality of life estimates and costs. A cost-effectiveness analysis was performed, more information on this specific analysis was previously described[18].

RESULTS

Patient characteristics

Between July 1, 2013 and August 31, 2014, a total of 3,666 patients met our inclusion and exclusion criteria and agreed to participate. Reasons for exclusion are depicted in Figure 4. Three patients (0.1%) withdrew from the study within 6 weeks and a total of 15 (0.4%) were lost to follow up. A total of 3,648 patients were included in the analysis: 1,827 in usual care and 1,821 in HEART care. Mean age was 62 years and 54% were male (Table 1). A low HEART score was calculated in 715 (39%) patients, an intermediate HEART score in 861 (47%), and a high HEART score in 190 (11%) of the patients. The HEART score was not calculated in 55 (3%) patients during HEART care.

Figure 4. Patient flow chart of the HEART-Impact trial – according to CONSORT guidelines

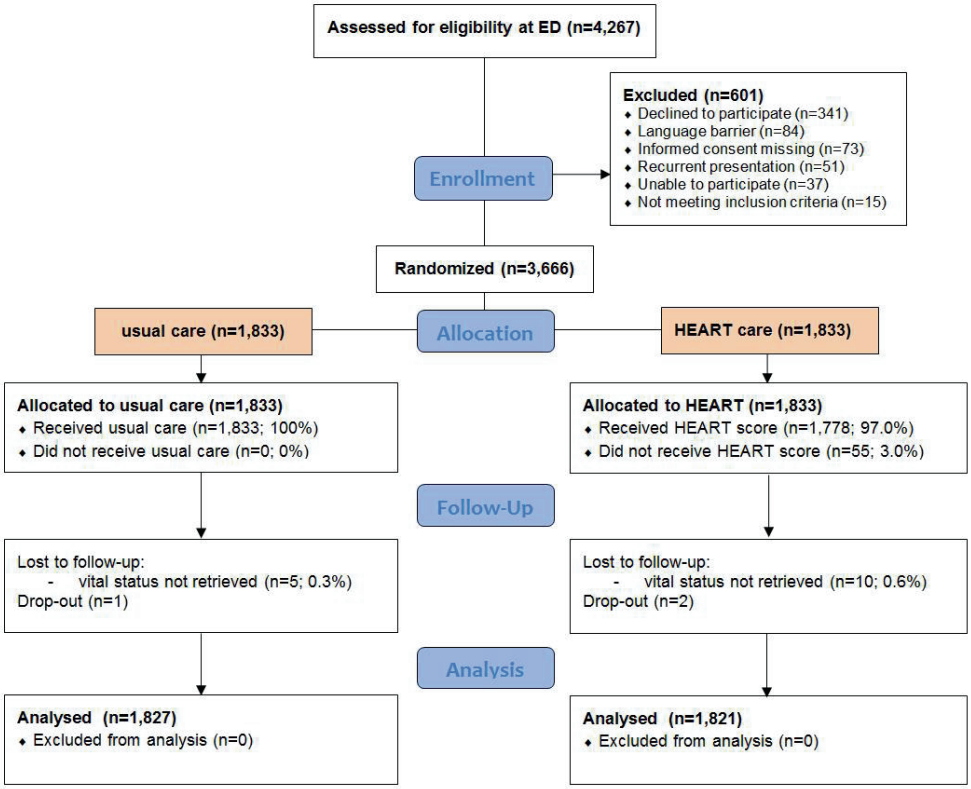


Table 1. Baseline characteristics of patients in the HEART-Impact trial

	HEART care (N=1,821)	Usual care (N=1,827)
Demographics		
Male	975 (54%)	1005 (55%)
Mean age (SD)	62 (14)	62 (14)
Vital signs at presentation		
Mean systolic blood pressure in mm Hg (SD)	144 (24)	143 (24)
Mean diastolic blood pressure in mm Hg (SD)	81 (13)	81 (13)
Mean heart frequency (SD)	73 (15)	74 (17)
Killip class I	1796 (99%)	1809 (99%)
Cardiac risk factors		
Diabetes Mellitus	285 (16%)	301 (16%)
Obesity (BMI>30)	327 (18%)	253 (14%)
Hypercholesterolemia	585 (32%)	683 (37%)
Hypertension	879 (48%)	926 (51%)
Positive family history	651 (36%)	599 (33%)
Current smoking	452 (25%)	444 (24%)
History of cardiovascular disease	596 (33%)	670 (37%)
History of AMI	288 (16%)	351 (19%)
History of PCI	344 (19%)	416 (23%)
History of CABG	131 (7%)	162 (9%)
History of CVA/TIA	101 (6%)	131 (7%)
History of peripheral artery disease	69 (4%)	77 (4%)
Laboratory results at presentation		
Mean creatinin (SD)	80 (33)	82 (31)
Medication at presentation		
Aspirin	621 (34%)	671 (37%)
P2Y12-inhibitor (clopidogrel)	109 (6%)	132 (7%)
Vitamin K antagonists (coumarin)	168 (9%)	190 (10%)
Other (Dipyridamol, Ticagrelor, DOAC)	69 (4%)	84 (5%)
HEART score		
HEART score 0-3 (low risk)	715 (39%)	-
HEART score 4-6 (intermediate risk)	861 (47%)	-
HEART score 7-10 (high risk)	190 (11%)	-
HEART score missing	55 (3%)	-

SD: standard deviation, mm Hg: millimetres of mercury, BMI: Body Mass Index, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary arterial bypass grafting, CVA: cerebrovascular attack, TIA: transient ischemic attack, DOAC: direct oral anticoagulant

Safety

The cumulative 6-week incidence of MACE was 18.9% during HEART care and 22.3% during usual care. The difference in MACE incidence (HEART care minus usual care) after adjustment for time steps and clustering was -1.3%, with a 95% one-sided upper confidence limit of +2.0%, demonstrating non-inferiority of HEART care as the non-inferiority margin was set at

3% (Figure 5). Adjustment for other prognostic factors did not meaningfully change the risk difference and none of the pre-specified subgroup analyses (women, elderly and diabetics) showed a statistically significant different effect of HEART care with respect to the incidence of MACE (data not shown). A total of 5 (0.3%) deaths occurred during HEART care and 9 (0.5%) during usual care. Further details on the components of MACE are provided in Table 2. The incidence of MACE in low-risk HEART patients was 2.0%, with one death of unknown cause occurring four weeks after initial presentation. This patient presented with atypical complaints and ECG and two troponin measurements were normal; the HEART score was calculated as 3, but should have been 4, since the patient was over 65 years and known with stroke. Detailed information on MACE in low-risk HEART care patients are provided in Appendix 3. The non-MACE group consisted of 2,900 (80%) patients, with a final diagnosis of this initial presentation of stable angina in 231 patients**,** rhythm disorders in 208 patients**,** heart failure 37 patients**,** pericarditis in 58 patients**,** and aspecific non-cardiac chest pain in 2,366 patients.

Figure 5. Non-inferiority of HEART care versus usual care

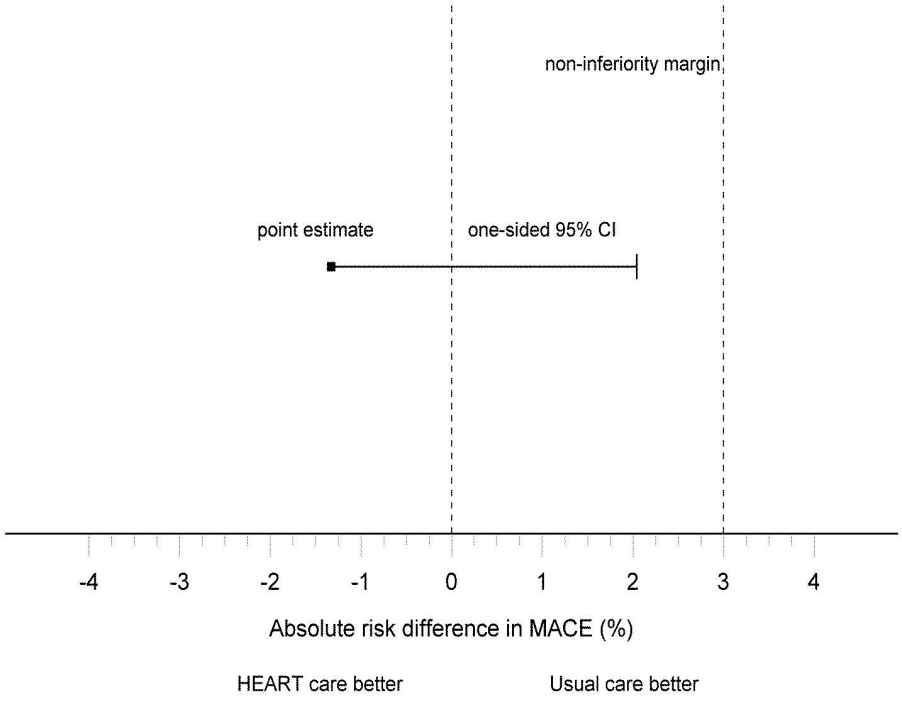


Table 2. Comparison 6-week incidence of MACE between usual care and HEART care

	Usual care (n=1,827)	**HEART care** (n=1,821)	HEART score 0-3 (n=715)	HEART score 4-6 (n=861)	HEART score 7-10 (n=190)	HEART unknown (n=55)
Number of patients with MACE	407 (22.3%)	345 (18.9%)	14 (2.0%)	175 (20.3%)	140 (73.7%)	16 (29.1%)
MACE - components*						
Death – total	9 (0.5%)	5 (0.3%)	1 (0.1%)	2 (0.2%)	2 (1.1%)	0 (0%)
Cardiovascular death	6	1	0	0	1	0
Non-cardiovascular death	0	1	0	0	1	0
Death by unknown cause**	3	3	1	2	0	0
Cardiac ischemia – total	399 (21.8%)	329 (18.1%)	10 (1.4%)	162 (18.8%)	143 (75.3%)	14 (25.4%)
Unstable angina	157	105	6	70	25	4
NSTEMI	213	211	4	91	107	9
STEMI	29	13	0	1	11	1
Significant stenosis – total	288 (15.8%)	243 (13.3%)	10 (1.4%)	116 (16.2%)	102 (11.8%)	15 (27.3%)
Stenosis managed conservatively	38	41	1	27	13	0
PCI	207	154	7	69	66	12
CABG	43	48	2	20	23	3
Total number of MACE	696	577	21	280	247	29

* total of MACE components exceeds MACE total: 1 patient can have more than 1 component

**including presumed acute cardiac death at home (no obduction performed)

***for more information on low-risk HEART patients see Appendix 3

MACE: major adverse cardiac events, NSTEMI: non-ST-elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, PCI: percutaneous coronary intervention, CABG coronary arterial bypass grafting

Use of health care resources

No major differences between HEART care and usual care were observed (Table 3). The proportion of early discharge at the ED within 4 hours was slightly higher during HEART care (34.37 vs. 30.64%, leading to a difference after adjustment for clustering and time steps 0.7%; 95% CI: -10.6 to +11.9%), but there was no difference in median length of stay (both 4 hours). In the low-risk patients, 648 (91%) were discharged from ED after initial presentation, although 232 (36%) of those were discharged after prolonged observation (>4h). Of the 9% low-risk HEART patients admitted to the hospital, 42 received a final diagnosis of aspecific chest pain, 18 patients a non-cardiac diagnosis (e.g. cholangitis or pleuritic pain) and 7 patients were diagnosed with cardiac ischemia. The total number of days of admission (3,085 vs. 3,365 days) and total number of initial admissions to the CCU during HEART care (355 vs. 430 admissions), as well as the median duration of stay after initial presentation (3 vs. 4 days) were lower in the HEART care than in the usual care group. After adjustment for clustering and time steps, no difference in readmissions, recurrent ED visits, or GP visits occurred. During HEART care an increase in out-patient clinic visits occurred (69.1 vs. 59.4%, leading to a difference adjusted for time steps and clustering of 1.9%; 95% CI: -6.2 to 8.5%). This increase consisted of visits to the cardiologist, but also to other out-patient clinics such as internal medicine. In addition, a small decrease in stress bicycle testing, nuclear testing and coronary angiography were observed during HEART care: this was not statistically significant after adjustment for clustering and time (Table 4).

Adherence to the HEART score policy

Physicians were asked to adhere to the formal recommendation of each HEART risk category, unless they felt this was not feasible or unsafe. Non-adherence meant (1) no discharge in low-risk patients, (2) no observation or non-invasive testing, or immediate invasive testing, in intermediate-risk patients, and (3) no intention for invasive treatment and diagnostic procedures in high-risk patients. In total, non-adherence occurred in 605/1,778 (34%) HEART care patients. This non-adherence occurred in 244/715 (34%) low-risk patients, in 314/861 (36%) intermediate-risk patients, and 47/190 (25%) high-risk patients. Reasons for non-adherence in low-risk patients were not given in 117 patients (47%), “gut feeling” in 70 patients (29%), alternative diagnosis being more probable in 33 patients (13%) and logistics in 27 patients (11%).

Table 3. Use of health care resources within 3 months after initial presentation within usual care and HEART care

	Usual care	HEART care	HEART score 0-3	HEART score 4-6	HEART score 7-10	HEART unknown
INFORMATION AVAILABLE IN ALL 9 HOSPITALS	n=1,827	n=1,821	n=715	n=861	n=190	n=55
Initial presentation at ED						
(1) (a) not admitted – no. (%)	1199 (66%)	1263 (69%)	648 (91%)	556 (65%)	29 (15%)	30 (55%)
Prompt discharge < 4h*	564 (47%)	633 (50%)	416 (64%)	190 (34%)	9 (31%)	18 (60%)
Prolonged observation at ED/CPU	635 (53%)	630 (50%)	232 (36%)	366 (66%)	20 (69%)	12 (40%)
Median length of stay at ED in hours (P25-P75)	3:57 (2:30-5:57)	3:55 (2:35-5:44)	3:16 (2:21-4:43)	4:40 (2:56-6:20)	3:32 (2:16-5:51)	2:57 (2:17-5:11)
(2) (b) hospital admission – no. (%)	628 (34%)	558 (31%)	67 (9%)	305 (35%)	161 (85%)	25 (45%)
Of which admission to CCU/ICU after ED	296 (47%)	223 (40%)	25 (37%)	104 (34%)	81 (50%)	13 (50%)
Median duration of stay in days (P25-P75)	4 (2-6)	3 (2-6)	2 (2-3)	3 (2-5)	4 (3-8)	4 (2-7)
Total number of days	3365	3085	193	1521	1228	143
Of which days on CCU / ICU	1032	880	44	360	435	41
≥ 1 recurrent visit at ED – no. (%)	266 (15%)	277 (15%)	72 (10%)	151 (18%)	46 (24%)	8 (15%)
Total number of visits	382	380	110	200	59	11
Final diagnosis – cardiac, ischemic	80	79	11	49	18	1
≥ 1 non-elective readmission – no. (%)	221 (12%)	193 (11%)	49 (10%)	104 (12%)	37 (19%	3 (5%)
Total number of readmissions	296	261	59	145	51	6
Median number of days (P25-P75)	2 (0-6)	2 (0-6)	2 (0-4)	2 (0-7)	2 (0-7)	2 (0-4)
≥ 1 out-patient clinic visit – no. (%)	1093 (60%)	1267 (70%)	381 (53%)	686 (80%)	165 (87%)	35 (64%)
Total number of visits	2730	3203	848	1823	443	89
Specialism cardiology	1505	1779	417	1034	267	61
Specialism other than cardiology	1225	1424	431	789	176	28
≥ 1 new visit at GP for cardiac reason – no. (%) **	195 (11%)	213 (12%)	86 (12%)	102 (12%)	18 (9%)	7 (13%)

ED: emergency department, CPU: chest pain unit, CCU: coronary care unit, ICU: intensive care unit, SD: standard deviation, GP: general practitioner * initial workup contains history taking, physical examination, 1st troponin and ECG, without further testing (e.g. 2nd troponin, stress test) ** Information obtained through 3-month telephone call, with 20% missing answers in usual care and 20% in HEART care

Table 4. Use of diagnostic procedures within 3 months in patients in the 5 hospitals participating in the cost-effective analysis

	Usual care N=1,176	**HEART care** N=804	**HEART 0-3** N=346	**HEART 4-6** N=361	**HEART 7-10** N=65	**HEART unknown** N=32
Number of patients with one or more of the tests mentioned in this table	765 (65%)	461 (57%)	137 (40%)	250 (69%)	56 (86%)	18 (56%)
Diagnostic testing – total numbers	1,565	940	228	541	136	35
Number of tests within first two days	582 (37%)	347 (37%)	49 (21%)	216 (40%)	65 (48%)	17 (49%)
Stress bicycle ECG testing**	465 (40%)	300 (37%)	96 (28%)	175 (48%)	18 (28%)	11 (34%)
Echocardiography (transthoracic)	410 (35%)	243 (30%)	50 (15%)	142 (39%)	43 (66%)	8 (25%)
Nuclear imaging	198 (17%)	89 (11%)	24 (7%)	56 (16%)	8 (12%)	1 (0%)
CT-scan of CT-angiography (excluding PE)	87 (7%)	47 (6%)	16 (5%)	27 (7%)	3 (5%)	1 (0%)
Coronary CT-Angiography (CCTA)	40 (3%)	26 (3%)	14 (4%)	10 (3%)	0 (0%)	2 (1%)
Cardiac MRI	19 (2%)	16 (2%)	6 (2%)	10 (3%)	0 (0%)	0 (0%)
Coronary angiography (CAG)	346 (29%)	219 (27%)	22 (6%)	121 (34%)	64 (98%)	12 (38%)
CAG: normal coronary arteries	41	19	4	13	2	0
CAG: non-significant stenosis	101	69	13	39	14	3
CAG: significant stenosis conservatively treated	28	15	0	12	3	0
CAG: significant stenosis invasively treated	176	116	5	57	45	9

Information on diagnostic testing is only available for patients included in the 5 hospitals participating in cost-effectiveness analysis

Quality of life, costs, and cost-effectiveness analysis

Quality of life scores obtained from the EQ-5D at baseline, 2 weeks and 3 months were 0.71, 0.73, 0.77 for HEART care and 0.70, 0.71, 0.73 for usual care, respectively. Health outcomes over the full 3 months following initial presentation, expressed as Quality-Adjusted Life Years (QALYs) per patient were 0.172 and 0.165 for HEART and usual care: a difference of 0.007 QALYs, 95%CI (0.001 to 0.012). QALYs calculated using the VAS scores were lower, but the difference was similar. Mean direct health care costs per patient were €3061 (95% CI: €2623 to 3527) and €3258 (95% CI: €2827 to 3762) for HEART and usual care: a difference of €−197 (95% CI: € −876 to 450). Given the improvement in health outcomes and the reduction in costs, HEART care was cost-effective and dominated usual care. However, differences in health outcomes and costs were small, with substantial remaining uncertainty. The probability that HEART dominated usual care equaled 71.0%, the probability that HEART was cost-effective for a Willingness-to-Pay (WTP) threshold of €20,000/QALY equaled 99.4%. Appendix 4 shows the results of the cost-effectiveness analysis.

DISCUSSION

In our stepped wedge cluster randomized trial comparing the application of the HEART score with usual care in chest pain patients, non-inferiority for the safety outcome MACE was demonstrated with a difference in the incidence of -1.3%, with a 95% one-sided upper confidence limit of +2.0%. More patients were discharged early within 4 hours after initial presentation (34.4% vs. 30.6%; difference after adjustment for clustering and time steps 0.7%; 95% CI: -10.6 to +11.9%). After adjustment for clustering and time steps, no difference in readmissions, recurrent ED visits, out-patient clinic visits, GP visits or diagnostic procedures occurred.

Our findings on safety are in line with several previous studies of the HEART score, in which the MACE incidences in the low-risk patients ranged from 0.6 to 1.7%[9-17]. Than et al. as well as Kline et al. describe false-negative rates of <1% or <2% to be acceptable for clinicians[24,25]. Although other risk scores have been developed and validated[26-29], to our knowledge none of them was tested in an impact study in daily practice. Advantages of the HEART score are that it is a very simple score (5 items, each with a score of 0, 1 or 2), and that it was developed specifically for chest pain patients. Furthermore, it identifies the largest proportion of patients as “low risk” eligible for early discharge from the ED without compromising safety[11,13-15]. Mahler et al. showed that the HEART score identified 20% of all patients (95% CI: 18–23%) for early discharge with 99% (95% CI: 97–100%) sensitivity for ACS[13]. In a small trial of 282 patients Mahler et al. compared the use of the HEART score to

usual care: objective cardiac testing at 30 days decreased by 12.1% (68.8% versus 56.7%; P=0.048) and length of stay by 12 hours (9.9 versus 21.9 hours; P=0.013). Early discharges increased by 21.3% (39.7% versus 18.4%; P<0.001). No patients identified for early discharge had MACE within 30 days[15].

Our trial has several strengths. This large impact trial included patients in a multicenter collaboration with several types of hospitals, making our results highly generalizable. Furthermore, this pragmatic trial is a reflection of the current real-life effect of the implementation of the HEART score, taking into account all possible intended and unintended effects of its use. Additionally, we had a complete follow-up in all but few patients (99.2%). Another feature of our study is the use of the stepped wedge design[30]. This design allows for the adjustment of changes occurring over time, which is not the case in a standard cluster randomized trial. The design also reduces the risk of contamination, compared to a trial including randomization at the patient level. Another strength of the study is that we ensured no HEART score was calculated during the usual care by instructing hospitals that they were going to switch to the HEART score very shortly before the actual switch to the HEART score. Additionally, we checked all admission charts and did not find documentation of HEART scores during usual care. Last, we included unstable angina and all revascularization procedures in our definition of MACE, since we wished to have a broad clinically relevant endpoint. Excluding unstable angina and elective revascularization would have decreased our low-risk MACE incidence to 1.0% (7/715).

Our study has several limitations. First, there may have been selective inclusion of patients during the HEART care and the usual care period which may affect the difference of MACE incidence between study periods, in case the selection process differs. This latter is, however, very unlikely. We did observe small changes in estimates when taking the effect of time into account. Adjustment for other known prognostic factors of MACE did not have an impact on the difference in MACE between HEART care and usual care. Second, we did not reach the number of patients calculated in our initial sample size calculations. This was mainly caused by withdrawal of one large participating hospital one week before the start of the trial and by the time constraints experienced at the ED to ask for informed consent. Also, the stepped wedge leads to a fixed number and length of steps reducing flexibility to add clusters or increase the inclusion period. Despite the lower number of inclusions, our study was still able to show non-inferiority: the non-inferiority margin was not exceeded. Also, there is no consensus on the optimal way to calculate the sample size for stepped wedge designs[31,32]. Third, since this was a pragmatic trial, usual care was not explicitly standardized. In order to partially account for this, we chose participating hospitals of various types and sizes.

There may be several possible reasons explaining the limited effect on health care utilization we observed. First, physicians calculated the score, but did not always adhere to the score's recommendation. A possible explanation for this non-adherence can be the difficulty to change behaviour. Getting familiar with calculations and adherence to a new algorithm takes time. The impact of the HEART score on health care utilization may become more prominent if it had been used for a longer period, with more low-risk patients being discharged at an earlier stage. In addition, there may have been a lack of trust in the safety of the score. This could also explain the increase of out-patient clinic visits during HEART care (although this was not statistically significant). Earlier studies showed that in patients with chest pain the rate of false-negatives is 6.4%[7], and the estimated incidence of unexpected sudden death is around 0.05-0.1%[33]. Accepting this inevitable risk is becoming less achievable in daily practice and poses a dilemma for both physician, patient and society[34]. A final reason for non-adherence to the recommendations could be the financial incentives of admission, testing and out-patient clinic visits.

Other types of protocols with cardiac markers or imaging have been advocated in the literature, for example a troponin protocol, in which the time interval to the second troponin assessment can be shortened to one hour after admission[8,35,36]. However, they include only myocardial infarction and death in their MACE definition, and, most importantly, the impact of the use of these protocols in real-life practice has not been studied. A possible adjustment of the HEART score to meet the current hesitation or skepticism to use the HEART score, would be to combine the calculation of the HEART score with this 1-hour troponin protocol. The use of coronary computed tomographic angiography (CCTA), a more invasive approach, has shown to reduce the length of stay[37,38], but CCTA does not result in better clinical outcomes than functional testing[39], and has not shown to date to be cost-effective when already a high-sensitive troponin (current daily practice) is used[8]. Moreover, a comparison of these and other studies with our study is difficult, since different populations were included and outcomes definitions or follow-up time varied.

We conclude that the HEART score is an accurate risk stratification instrument, and safe to use when assessing patients with chest pain. The full potential of the HEART score in terms of considerable reductions in health care costs was not achieved in our trial. This is possibly due to hesitance to refrain from admitting patients and additional testing in case of patients with low scores. If such barriers are addressed and patient management would be guided by the HEART score, a more considerable effect on health care costs might be achieved.

COMPETING INTERESTS

Two authors (BEB and AJS) were involved in the development of the HEART score. The authors declare that they have no other competing interests.

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REFERENCES

1. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart. 2005;91(2):229-30.
2. Pitts SR, Niska RW, Xu J, Burt CW. National Hospital Ambulatory Medical Care Survey: 2006 emergency department summary. Natl Health Stat Report. 2008;7:1–38.
3. Owens PL, Barrett ML, Gibson TB, Andrews RM, Weinick RM, Mutter RL. Emergency department care in the United States: a profile of national data sources. Ann Emerg Med. 2010;56:150–165.
4. Lee TH, Goldman L. Evaluation of the patient with acute chest pain. N Engl J Med 2000, 342:1187–1195.
5. Carlton EW, Than M, Cullen L, Khattab A, Greaves K. 'Chest Pain Typicality' in Suspected Acute Coronary Syndromes and the Impact of Clinical Experience. Am J Med. 2015;128(10):1109-1116.e2.
6. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000;342:1163-70.
7. Christenson J, Innes G, McKnight D, Boychuk B, Grafstein E, Thompson CR, et al. Safety and efficiency of emergency department assessment of chest discomfort. CMAJ 2004;170:1803-7.
8. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2015 Aug 29. pii: ehv320.2015.
9. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J 2008;16:191-6.
10. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room; a multicenter validation of the HEART score. Crit Path Cardiology 2010;9:164-169.
11. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol. 2013;168(3):2153-8.
12. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART Score for the Assessment of Patients With Chest Pain in the Emergency Department: A Multinational Validation Study. Crit Pathways in Cardiol 2013;12:121–126.
13. Mahler SA, Hiestand BC, Goff DC Jr, Hoekstra JW, Miller CD. Can the HEART score safely reduce stress testing and cardiac imaging in patients at low risk for major adverse cardiac events? Crit Pathw Cardiol. 2011;10(3):128-33.
14. Mahler SA, Miller CD, Hollander JE, Nagurney JT, Birkhahn R, Singer AJ, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. Int J Cardiol. 2013;168(2):795-802.
15. Mahler SA, Riley RF, Hiestand BC, Russell GB, Hoekstra JW, Lefebvre CW, et al. The HEART Pathway randomized trial: identifying emergency department patients with acute chest pain for early discharge. Circ Cardiovasc Qual Outcomes. 2015;8(2):195-203.
16. Melki D, Jernberg T. HEART score: a simple and useful tool that may lower the proportion of chest pain patients who are admitted. Crit Pathw Cardiol. 2013;12(3):127-31.
17. Carlton EW, Khattab A, Greaves K. Identifying Patients Suitable for Discharge After a Single-Presentation High-Sensitivity Troponin Result: A Comparison of Five Established Risk Scores and Two High-Sensitivity Assays. Ann Emerg Med. 2015. pii: S0196-0644(15)00583-1.
18. Poldervaart JM, Reitsma JB, Koffijberg H, Backus BE, Six AJ, Doevendans PA, et al. The impact of the HEART risk score in the early assessment of patients with acute chest pain: design of a stepped wedge, cluster randomised trial. BMC Cardiovascular Disorders 2013;13:77.
19. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ. 2015;350:h391.

20. Kappen TH, Vergouwe Y, van Wolfswinkel L, Kalkman CJ, Moons KG, van Klei WA. Impact of adding therapeutic recommendations to risk assessments from a prediction model for postoperative nausea and vomiting. Br J Anaesth. 2015;114(2):252-60.
21. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD. Third Universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60(16):1581–98.
22. Richtlijnen voor farmaco-economisch onderzoek – geactualiseerde versie 2006 [Guidelines for pharmaco-economic research]. Diemen: College voor Zorgverzekeringen (CvZ) [Health Insurance Board]; 2006.
23. Hubbard AE, Ahern J, Fleischer NL, Van der Laan M, Lippman SA, Jewell N, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology. 2010;21(4):467-74.
24. Than M, Herbert M, Flaws D, Cullen L, Hess E, Hollander JE, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. Int J Cardiol. 2013;166(3):752-4.
25. Kline JA, Johnson CL, Pollack Jr CV, Diercks DB, Hollander JE, Newgard CD, et al. Pretest probability assessment derived from attribute matching. BMC Med Inform Decis Mak 2005;5:26.
26. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Archives of internal medicine. 2003;163:2345-53.
27. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook G, et al. The Manchester acute coronary syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. Heart. 2014;100(18):1462-8.
28. Antman EM, Cohen M, Bernink PJLM, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI; a method for prognostication and therapeutic decision making. JAMA. 2000;284:835-42.
29. Christenson J, Innes G, McKnight D, Thompson CR, Wong H, Yu E, et al. A clinical prediction rule for early discharge of patients with chest pain. Annals of emergency medicine. 2006;47: 1-10.
30. Beard E, Lewis JJ, Copas A, Davey C, Osrin D, Baio G, et al. Stepped wedge randomised controlled trials: systematic review of studies published between 2010 and 2014. Trials. 2015;16(1):353.
31. Baio G, Copas A, Ambler G, Hargreaves J, Beard E, Omar RZ. Sample size calculation for a stepped wedge trial. Trials. 2015;16(1):354.
32. Davey C, Hargreaves J, Thompson JA, Copas AJ, Beard E, Lewis JJ, et al. Analysis and reporting of stepped wedge randomised controlled trials: synthesis and critical appraisal of published studies, 2010 to 2014. Trials. 2015;16(1):358.
33. John RM, Tedrow UB, Koplan BA, Albert CM, Epstein LM, Sweeney MO, et al. Ventricular arrhythmias and sudden cardiac death. Lancet. 2012;380(9852):1520-9.
34. Brace-McDonnell SJ, Laing S. When is low-risk chest pain acceptable risk chest pain? Heart. 2014;100(18):1402-3.
35. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med. 2012;172(16):1211-8.
36. Rubini Gimenez M, Twerenbold R, Jaeger C, Schindler C, Puelacher C, Wildi K, et al. One-hour Rule-in and Rule-out of Acute Myocardial Infarction Using High-sensitivity Cardiac Troponin I. Am J Med. 2015;128(8):861-870. e4.
37. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med. 2012;366(15):1393-403.
38. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med. 2012 Jul 26;367(4):299-308.
39. Douglas PS, Hoffmann U. Anatomical versus Functional Testing for Coronary Artery Disease. N Engl J Med. 2015;373(1):91.

Appendix 1. Characteristics of troponin kits and cut-offs of hospitals in the HEART-Impact trial

Hospital	Type of troponin	Type of troponin T or I	Analyzer	Cut-off value
Hospital 1	conventional	I	Siemens dimension vista	45 ng/l
Hospital 2	conventional	I	Beckman Coulter DxI	40 ng/l
Hospital 3	high sensitive	T	Roche modular	14 ng/l
Hospital 4	high sensitive	T	Roche Cobass	10 ng/l
Hospital 5	conventional	I	Beckman Coulter DxI	60 ng/l
Hospital 6	high sensitive	T	Roche Cobass	14 ng/l
Hospital 7	high sensitive	T	Roche Cobass	30 ng/l + delta >8ng
Hospital 8	high sensitive	T	Roche modular	50 ng/l
Hospital 9	high sensitive	T	Roche Cobass	14 ng/l

Appendix 2. Characteristics of participating hospitals in the HEART-Impact trial

Hospital	Type	Size: number of beds	Revascularation options in own hospital
Hospital 1	peripheral	505*	No
Hospital 2	peripheral	262*	No
Hospital 3	academic	733	PCI and CABG
Hospital 4	peripheral	1,230**	PCI
Hospital 5	academic	1,042**	PCI and CABG
Hospital 6	peripheral	1,102	PCI and CABG
Hospital 7	peripheral	550**	PCI and CABG
Hospital 8	peripheral	378**	No
Hospital 9	peripheral	255	No

* in 2012
** in 2013
PCI: percutaneous coronary intervention, CABG coronary arterial bypass grafting, ED Emergency department

Appendix 3. Detailed characteristics of low-risk HEART patients with MACE within 6 weeks

Patient	Age	Gender	H	E	A	R	T	Total HEART	Troponin 1*	Troponin 2*	MACE	ED - date	MACE - date
1	58	male	1	0	1	0	0	2	under	under	UA; CABG	7-09-13	7-09-13; 16-10-13
2	42	male	1	0	0	1	0	2	under	under	**NSTEMI**; PCI**	4-06-14	4-06-14; 5-06-14
3	46	male	1	0	1	0	0	2	under	under	PCI	15-11-13	9-12-13
4	46	male	1	0	1	0	1	3	above	above	**NSTEMI**	7-04-14	7-04-14
5	61	female	1	0	1	1	0	3	under	above	**NSTEMI**	30-06-14	30-06-14
6	67	female	0	0	2	1	0	3	under	under	**Death - unknown cause**	15-07-14	13-08-14
7	65	male	1	0	1	1	0	3	under	above	UA; CABG	18-04-14	18-04-14; 29-04-14
8	56	male	1	0	1	1	0	3	under	not performed	UA (no CA performed)	24-02-14	24-02-14
9	49	male	0	0	1	2	0	3	under	not performed	**UA; PCI**	8-07-14	8-07-14; 10-07-14
10	56	male	1	0	1	1	0	3	under	not performed	UA; PCI	2-06-14	2-06-14; 14-07-14
11	49	male	0	0	1	2	0	3	under	under	PCI	3-07-14	23-07-14
12	60	male	0	0	1	2	0	3	under	under	CAG-conservative	1-07-14	29-07-14
13	41	female	1	0	0	1	1	3	above	above	**NSTEMI**	20-02-14	20-02-14
14	62	male	1	0	1	1	0	3	under	not performed	**UA; PCI**	19-03-14	19-03-14; 2-04-14

* troponin measurements under or above the 99th percentile
** Troponin 3 = 77 ng/l
bold = Only NSTEMI, STEMI, Emergency revascularization and death

Appendix 4. Results of the cost-effectiveness analysis

	Usual care Complete cases (n=990)	HEART care Complete cases (n=665)	Difference[1] Complete cases	Usual Care after MI[2]	Heart care after MI	Difference after MI
Quality of life[3] – baseline (mean, 95% CI[4])	0.71 (0;1)	0.71 (0.10; 1.00)	0.005	0.70 (0.69; 0.72)	0.71 (0.69; 0.73)	0.005 (-0.018; 0.028)
Quality of life – 2 weeks (mean, 95% CI)	0.71 (0.03; 1.00)	0.74 (0.06; 1.00)	0.020	0.71 (0.69; 0.73)	0.73 (0.71; 0.75)	0.022 (-0.005; 0.0049)
Quality of life – 3 months (mean, 95% CI)	0.73 (0.03; 1.00)	0.77 (0.16; 1.00)	0.037	0.73 (0.71; 0.75)	0.77 (0.75; 0.79)	0.042 (0.013;0.069)
Quality of life (after 3 months) (mean, 95% CI)	8.66 (1.43; 12.00)	8.99 (2.26; 12.00)	0.33	8.60 (8.42; 8.78)	8.95 (8.74; 9.15)	0.35 (0.063; 0.615)
Quality of adjusted life years (mean, 95% CI)	0.166 (0.027; 0.230)	0.172 (0.043; 0.230)	0.006	0.16 (0.16; 0.17)	0.17 (0.17; 0.18)	0.007 (0.001; 0.012)
Costs – total (after 3 months)[5] (mean, 95% CI)	3256 (8; 20405)	3070 (8; 23718)	−186	3258 (2827; 3762)	3061 (2623; 3527)	−197 (−876; 450)

[1] Difference is defined by heart care minus usual care
[2] MI: multiple imputation
[3] Quality of life is measured by the EQ5D
[4] CI: confidence interval; quantile interval because of non-normality
[5] Costs on diagnostic testing, lab tests, inpatient hospital days (normal, intensive care unit and cardic care unit), visits to the general practice

R1 R2 R3 R4 R5 R6 R7 R8 R9 R10 R11 R12 R13 R14 R15 R16 R17 R18 R19 R20 R21 R22 R23 R24 R25 R26 R27 R28 R29 R30 R31 R32 R33 R34 R35 R36 R37 R38 R39

Quality of life is shown for complete cases and after imputation with a bootstrap sample of 2500 bootstraps.

a) Utility – EQ5D

N=1768	0 weeks	2 weeks	12 weeks
Complete cases	N=1655	N=1211	N=1128
Mean CC Usual Care (sd)	0.71 (0.26)	0.71 (0.25)	0.73 (0.25)
Mean CC HEART	0.71 (0.24)	0.74 (0.24)	0.77 (0.23)
Mean difference*	0.01	0.02	0.04
Missing values USUAL	64 (6.1%)	324 (30.7%)	391 (37.1%)
Missing values HEART	49 (6.9%)	233 (32.6%)	249 (55.9%)
Multiple imputation (m=10)			
Mean usual	0.70	0.71	0.73
Mean heart	0.71	0.73	0.77
Mean difference*	0.005	0.022	0.042
Bootstrap (x=2500)			
SE of difference*	0.012	0.014	0.014
95 % quantile (difference*)	(-0.018; 0.028)	(-0.005; 0.049)	(0.013;0.069)

* Difference is defined as heart intervention − usual care

b) VAS score

N=1768	0 weeks	2 weeks	12 weeks
Complete cases	N=1630	N=1210	N=1127
Mean Usual Care (sd)	58.53 (18.0)	67.30 (18.85)	68.89 (18.24)
Mean CC HEART	58.55 (16.6)	67.37 (19.10)	70.69 (16.76)
Mean difference*	0.02	0.07	1.80
Missing values USUAL	88 (8.3%)	325 (30.8%)	394 (37.3%)
Missing values HEART	50 (7.0%)	233 (32.6%)	247 (55.7 %)
Multiple Imputation (m=10)			
Mean usual	58.53	66.97	68.45
Mean heart	58.74	66.47	70.37
Mean difference*	0.204	-0.504	1.919
Bootstrap (x=2500)			
SE of difference*	0.849	1.132	1.055
95 % quantile (difference*)	(-1.469; 1.874)	(-2.651; 1.695)	(-0.156; 3.975)

* Difference is defined as heart intervention − usual care

c) Quality adjusted life months/years

N=1768	QoL after 12 weeks	QALYs
Complete cases	N=942	N=942
Mean CC Usual Care (sd)	8.66	0.16
Mean CC HEART	8.99	0.17
Mean difference*	0.33	0.0062
Missing values USUAL	487 (46.2%)	487 (46.2%)
Missing values HEART	339 (47.5%)	339 (47.5%)
Multiple imputation (m=10)		
Mean usual	8.60	0.165
Mean heart	8.96	0.172
Mean difference*	0.35	0.007
Bootstrap (x=2500)		
SE of difference*	0.142	0.003
95 % quantile (difference)	(0.063; 0.615)	(0.001; 0.012)

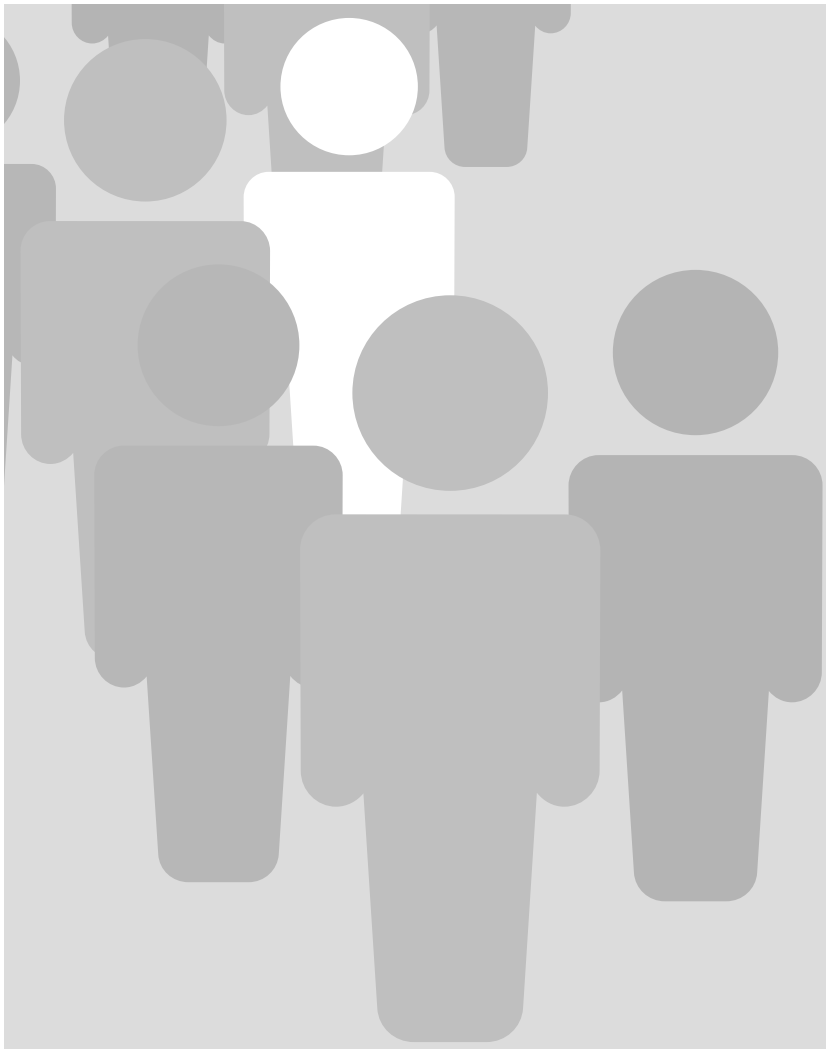
Number of ED visits for chest pain problems; 200000 (2013) (10% of the 2.0 million ED visits in 2013 in the Netherlands)

d) Costs

N=1768	After 12 weeks
Multiple imputation (m=10)	
Mean usual	3258.39
Mean heart	3061.31
Mean difference*	-197.08
Bootstrap (x=2500)	
SE of difference*	335.78
95 % quantile (difference*)	(-876.20; 450.39)

e) Cost-effectiveness

	Probability
Better and cheaper	0.710
Better and more expensive	0.284
Worse but cheaper	0.003
Worse and more expensive	0.004



Comparison of the performance of the GRACE, HEART and TIMI score to predict acute coronary syndrome in patients presenting with chest pain at the emergency department

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Submitted

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ABSTRACT

Background: Cardiac risk scores have been developed to improve risk stratification in patients presenting with chest pain at the emergency department (ED). We compared the performance of the GRACE, HEART and TIMI scores in predicting the probability of acute coronary syndrome (ACS) in patients presenting with chest pain at the ED.

Methods: Patients presenting with chest pain at the ED, included in the HEART-impact trial in nine Dutch hospitals, were included in the analysis. The primary outcome was major adverse cardiac events (MACE) within 6 weeks. The HEART score was determined by the treating physician during presentation at the ED. The GRACE and TIMI score were calculated based on routinely collected data. The performance of the scores was compared by calculating areas under the ROC curves (AUC). In addition, we compared the number of low-risk patients identified by each score as well as the safety (i.e. the incidence of MACE in low-risk patients), defining safety as missing no more than 5% of all patients with MACE (scenario I) or missing no more than 2% of all patients with MACE (scenario II).

Results: In total, 1,748 (54% male, mean age 62) were included. The 6-week cumulative incidence of MACE was 19%. The AUC of GRACE, HEART, and TIMI were, 0.73 (95% CI: 0.70-0.76%), 0.86 (95% CI: 0.84-0.88%) and 0.80 (95% CI: 0.78-0.83%), respectively. The differences in AUC were highly statistically significant. At an absolute level of safety of missing no more than 5% of all patients with MACE, the GRACE score identified 334 patients as “low risk” while in 12/334 (3.6%) patients a MACE was missed; the HEART score identified 708 patients as “low risk” with 14/708 (2.0%) missed MACE. The TIMI score identified 439 “low risk” patients with 15/439 (3.4%) missed MACE.

Conclusion: The HEART score outperformed the GRACE and TIMI scores in discriminating between those with and without ACS in patients with chest pain. In addition, the HEART score identifies the largest group of low-risk patients without compromising safety.

BACKGROUND

Up to 6.3% of emergency department (ED) visits are related to chest pain[1]. An urgent question in these patients is whether they have acute coronary syndrome (ACS), as any delay in diagnosis and treatment can have a negative impact on their prognosis[2-4]. Normal values of troponin and a normal electrocardiogram (ECG) still do not exclude ACS completely. As a result, the majority of patients presenting with chest pain are currently hospitalized and extensively evaluated with non-invasive stress testing or imaging, or with an invasive coronary angiography[5]. However, of all chest pain patients less than 25% will have an ACS[5]. If patients at low risk for ACS could be recognized early in the diagnostic process, it has the potential to reduce patient burden, length of stay at the ED, frequency of hospitalization and costs[6-8].

To diagnose ACS, physicians use patient history, ECG abnormalities, cardiac markers (notably troponin) and several other potential variables[2,9]. International cardiac guidelines state that chest pain patients presenting to the ED should be assessed with a risk stratification tool or risk score[2,10,11] and over the years, a number of tools have been developed[12-20]. Three well-known risk scores are the GRACE score, the HEART score and the TIMI score, see Table 1 and Appendix 1[15,16,19]. Risk scores combine and weigh various predictors to calculate the risk of ACS for an individual patient. They are based on readily available information collected during the initial work-up of chest pain patients.

Studies directly comparing the performance of risk scores in the same population of chest pain patients are rare and typically, the sample sizes of these studies are small[21-24]. Furthermore, it is unclear which risk score performs best in identifying patients at low risk of ACS, as these patients are candidates for early discharge from the ED (triage role). Therefore, we compared the performance of the GRACE, HEART and TIMI risk scores in identifying ACS in patients presenting with chest pain at the ED.

METHODS

Study population

Our study population consisted of patients participating in the HEART-impact trial. In short, this trial investigated the impact of the use of the HEART score in daily practice on safety, quality of life and use of health care resources. The trial was designed as a pragmatic, stepped wedge, cluster randomized trial and compared usual care with HEART score care (i.e. calculation of the HEART score and adherence to recommended patient management

depending on the score; see Appendix 2 and[25]. Any patient with chest pain presenting to the ED was eligible for inclusion. Patients that were directly recognized as having STEMI were excluded, because of the lack of diagnostic uncertainty. All included patients provided written informed consent. Further details can be read in the published study protocol[25]. For our current study, we only analyzed patients who were included during the HEART care period (half of the original study population), since specific measures were taken during the usual care period of the HEART-Impact trial to ensure the HEART score was not calculated.

Endpoints

The main endpoint in our study was major adverse cardiac events (MACE) within 6 weeks after the initial ED presentation. MACE consisted of unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), percutaneous coronary intervention (PCI), coronary arterial bypass grafting (CABG), stenosis managed conservatively, cardiovascular death, non-cardiovascular death and death with unknown cause. The potential occurrence of MACE was identified by means of a phone call with each patient at 3 months after presentation[25]. In case the patient could not be contacted, the patient's general practitioner was contacted and the electronic hospital records were investigated. All information possibly indicating MACE was further investigated by examining medical records from the hospital and/or the general practitioner. All potential events were then adjudicated by two independent cardiologists and it was decided whether a MACE occurred or not. The adjudication was done blinded for the GRACE, HEART and TIMI scores[25].

Calculation of the risk scores

All variables used in the risk scores were collected at time of presentation at the ED and are depicted in Table 1. The GRACE score and TIMI score were calculated automatically from the recorded data, without interpretation by the investigators. The HEART score was calculated by physicians at the moment of admission at the ED during the HEART care period[25].

Statistical analysis

Continuous variables were presented as means with standard deviations, categorical variables were presented as absolute number of patients with corresponding percentages. Cut-off values of troponin were provided by all participating hospitals to assess whether the level of this cardiac marker was elevated. We compared the discrimination of the three scores by examining their ROC curves and calculating the areas under the ROC curve (AUCs), also known as the c-statistic, and the corresponding 95% confidence intervals (CI). To compare the c-statistics we used the method of DeLong[26], which takes into account the paired nature of our data as all three scores were determined in each patient. One of the key roles of these risk scores is to identify patients at low risk for MACE. Therefore, we compared the number of patients identified as "low risk" at a fixed level of safety. In our

baseline scenario we calculated the cut-off for each risk score with an absolute safety level of no more than 5% of all patients with MACE being missed. The risk score with the highest number of patients identified as low risk considering this safety level can then be considered the most efficient score. We considered an alternative scenario with an absolute safety level of missing not more than 2% of all patients with MACE. Both the baseline and alternative scenario of safety levels were based on the first measurement of troponin at the ED. To reflect current clinical practice most closely, we also calculated all three scores based on the first and (when available) second troponin measurement and again assessed the scores' efficiency and safety. Furthermore, to facilitate comparison with other studies, we also assessed the efficiency and safety, when the primary endpoint of MACE consisted of only AMI and/or death. We used Statistical Package for the Social Sciences (IBM SPSS statistics, version 21) for all statistical analyses, except for the comparison of the paired ROC curves and AUC for which we used SAS version 9.1.

Table 1. Variables present in GRACE score, HEART score and TIMI score

Variables		GRACE score	HEART score	TIMI score
Age		X	X	X
Gender				
History	Suspicious (physicians' opinion)		X	
	Severe angina (≥2 events in last 24h)			X
	Use of aspirin last 7 days			X
	Killip class	X		
Physical examination	Heart rate	X		
	Systolic blood pressure	X		
ECG	ST deviation	X	X	X
	Repolarization disorder, LBBB or pacemaker		X	
	Cardiac arrest at admission	X		
Laboratory results	Creatinin level	X		
	Positive cardiac enzyme[$]	X	X	X
Risk factors	Previous atherosclerotic disease[#]		X	
	Previous coronary artery disease			X
	Prior coronary artery stenosis ≥50%			X
	Current smoking*		X	X
	Diabetes mellitus		X	X
	Family history of cardiovascular disease		X	X
	Hypercholesterolemia		X	X
	Hypertension		X	X
	Obesity (body mass index >30)		X	

ECG: electrocardiogram, LBBB: left bundle branch block
[$] troponin or creatin kinase–MB
previous atherosclerotic disease was defined as myocardial infarction, coronary arterial bypass grafting, percutaneous coronary intervention, stroke or transient ischemic attack, peripheral artery disease
***** smoking in the HEART –impact trial was defined as smoking currently or stopped < 3 months

RESULTS

Study population

Patients were enrolled between July 1, 2013 and August 31, 2014 in nine hospitals in the Netherlands. For patient flow see Figure 1. In total 3,666 patients were included in the HEART-Impact trial, with 1,833 (50%) patients included during HEART care period. Of these 1,833 HEART care patients, 10 patients (0.5%) were lost to follow-up, and 2 patients (0.1%) withdrew their informed consent. In 20 patients (1.1%) the GRACE score could not be calculated due to missing creatinin or systolic blood pressure levels. The HEART score was not calculated by the physician at ED in 55 patients (3.0%). The TIMI score could be calculated in all patients. In a total of 73 (4.0%) patients, one or more risk score could not be calculated and therefore 1,748 patients were used in the analysis. The mean age of these patients was 62 years and 54% was male. Patient characteristics are shown in Table 2.

Figure 1. Patient flow chart for patients included in current comparison of performance of the GRACE score, HEART score and TIMI score

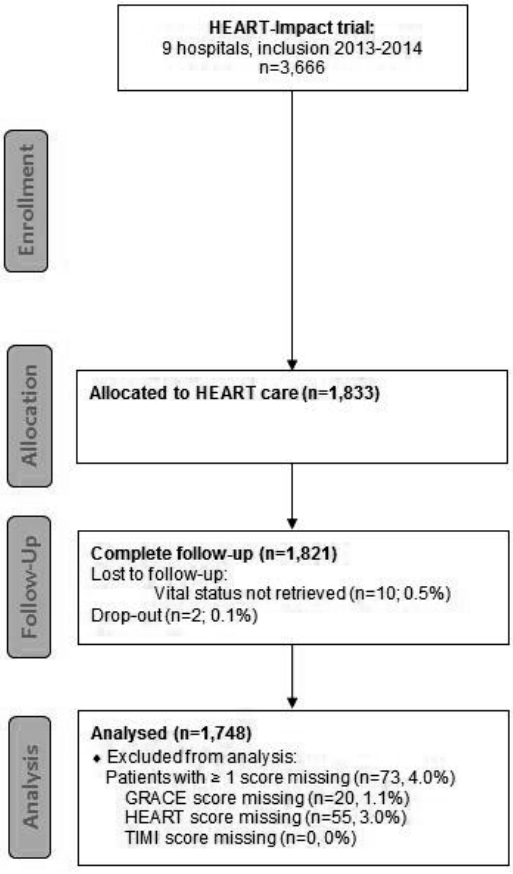


Table 2. Baseline characteristics

	All patients (n=1,748)	Patients with MACE (n=326)	Patients without MACE (n=1,422)
Demographics			
Male	937 (54%)	227 (70%)	710 (50%)
Mean age (SD)	62 (14)	67 (11)	60 (15)
Vital signs at presentation:			
Mean systolic blood pressure in mm Hg (SD)	144 (23)	147 (23)	143 (23)
Mean diastolic blood pressure in mm Hg (SD)	81 (13)	82 (13)	81 (13)
Mean heart frequency (SD)	73 (15)	75 (17)	73 (15)
Killip class I	1723 (99%)	317 (97%)	1406 (99%)
Cardiac risk factors			
Diabetes Mellitus	271 (16%)	68 (21%)	203 (14%)
Obesity (BMI >30)	319 (18%)	58 (18%)	261 (18%)
Hypercholesterolemia	559 (32%)	117 (36%)	442 (31%)
Hypertension	846 (48%)	209 (64%)	637 (48%)
Positive family history	629 (36%)	117 (36%)	512 (36%)
Current smoking	441 (25%)	81 (25%)	360 (25%)
History of cardiovascular disease*	576 (33%)	154 (47%)	422 (30%)
History of AMI	277 (16%)	65 (20%)	212 (15%)
History of PCI	331 (19%)	91 (28%)	240 (17%)
History of CABG	128 (7%)	36 (11%)	92 (6%)
History of CVA/TIA	98 (6%)	27 (8%)	71 (5%)
History of peripheral artery disease	69 (4%)	25 (8%)	44 (3%)
Laboratory results at presentation			
Mean creatinin (SD)	80 (33)	85 (22)	78 (35)
Medication at presentation			
Aspirin	597 (34%)	153 (47%)	444 (31%)
P2Y12-inhibitor (clopidogrel)	107 (6%)	40 (12%)	67 (5%)
Vitamin K antagonists (coumarin)	162 (9%)	33 (10%)	129 (9%)
Other (Dipyridamol, Ticagrelor, DOAC)	62 (4%)	14 (4%)	48 (3%)

SD: standard deviation, mm Hg: millimetres of mercury, bpm: beats per minute, BMI: Body Mass Index, AMI: acute myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary arterial bypass grafting, CVA: cerebrovascular attack, TIA: transient ischemic attack, DOAC: direct oral anticoagulant

Endpoints

A total of 543 MACE occurred in 326 (19%) patients, consisting of 99 (6%) UA, 201 (11%) NSTEMI, 11 (1%) STEMI, 41 (2%) stenosis managed conservatively, 141 (8%) PCI, 45 (3%) CABG, 1 (0.1%) cardiovascular death, 1 (0.1%) non-cardiovascular death and 3 (0.2%) deaths from an unknown cause.

Performance of the risk scores

In Figure 2, the ROC curves of the GRACE score, HEART score and TIMI score are shown. The AUC of the HEART score was highest with 0.86 (95% CI: 0.84-0.88), followed by the AUC of the TIMI score with 0.80 (95% CI: 0.78-0.83) and the GRACE score with an AUC of 0.73 (95% CI: 0.70-0.76). All differences in AUC were highly statistically significant: all p-values <0.001. Table 3 shows the comparison of performance of GRACE, HEART and TIMI score in terms of safety and efficiency, using only the first troponin measurement taken during the initial assessment at the ED. Scenario I used an absolute level of safety of missing no more than 5% of all patients with MACE to define a "low-risk" group. At this absolute safety level, the GRACE score classified 334 patients as "low risk" of whom 12/334 (3.6%) patients developed MACE. Using the same absolute safety level, the HEART score classified 708 patients as "low risk" with 14/708 (2.0%) patients developing MACE. Lastly, the TIMI score identified 439 patients as "low risk" with 15/439 (3.4%) having a MACE.

We repeated the analyses at a different absolute safety level of missing no more than 2% of MACE in all patients with MACE (scenario II). This sensitivity analysis showed that the HEART score again was the more efficient score with a low-risk group of 381 patients versus 231 and no patients for the GRACE and TIMI scores, respectively. The proportion of MACE in these low-risk groups were 0.9% and 2.2% for respectively the HEART and GRACE scores. Furthermore, to facilitate comparison with other studies, we also identified the number of patients with an acute myocardial infarction (AMI) or death, which are shown in Table 3. To reflect current clinical practice with serial troponin measurements closely, Table 4 shows the comparison of performance of GRACE, HEART and TIMI score, in terms of safety and efficiency, based on the first and second troponin measurement (when performed). At the absolute safety level of 5%, the GRACE score classified 340 patients as "low risk" of whom 14/340 (4.1%) patients developed MACE. Using the same absolute safety level, the HEART score classified 707 patients as "low risk" with 13/707 (1.8%) patients developing MACE. Lastly, the TIMI score identified 430 patients as "low risk" with 8/430 (1.9%) having a MACE. Repeating this for the 2% absolute safety level for total missed MACE resulted in MACE in the low-risk groups of 2.5% (6/243) and 0.8% (3/381) for the GRACE and HEART score, respectively. The TIMI score did not have a low-risk group within this limit of 2% total missed MACE.

Table 3. Comparison of performance of GRACE score, HEART score and TIMI score in terms of safety and efficiency based on first troponin measurement

<5.0% patients identified with MACE of total patients with MACE	**GRACE score**	**HEART score**	**TIMI score**
Corresponding cut-off for "low risk"	≤72 points	≤3 points	0 points
Actual number of patients with MACE in "low risk" group / total patients with MACE	12/326 (3.7%)	14/326 (4.3%)	15/326 (4.6%)
Of which AMI	4	3	6
Of which death	0	1	0
Number of patients classified as "low risk" / total number of patients	334/1748 (19.1%)	708/1748 (40.5%)	439/1748 (25.1%)
Percentage of MACE in "low risk" group	3.6% (12/334)	2.0% (14/708)	3.4% (15/439)
<2.0% patients identified with MACE of total patients with MACE	**GRACE score**	**HEART score**	**TIMI score**
Corresponding cut-off for "low risk"	≤66 points	≤2 points	-*
Actual number of patients with MACE in "low risk" group / total patients with MACE	5/326 (1.5%)	3/326 (0.9%)	-
Of which AMI	1	1	-
Of which death	0	0	-
Number of patients classified as "low risk" / total number of patients	231/1748 (13.2%)	381/1748 (21.8%)	-
Percentage of MACE in "low risk" group	2.2% (5/231)	0.5% (2/381)	-

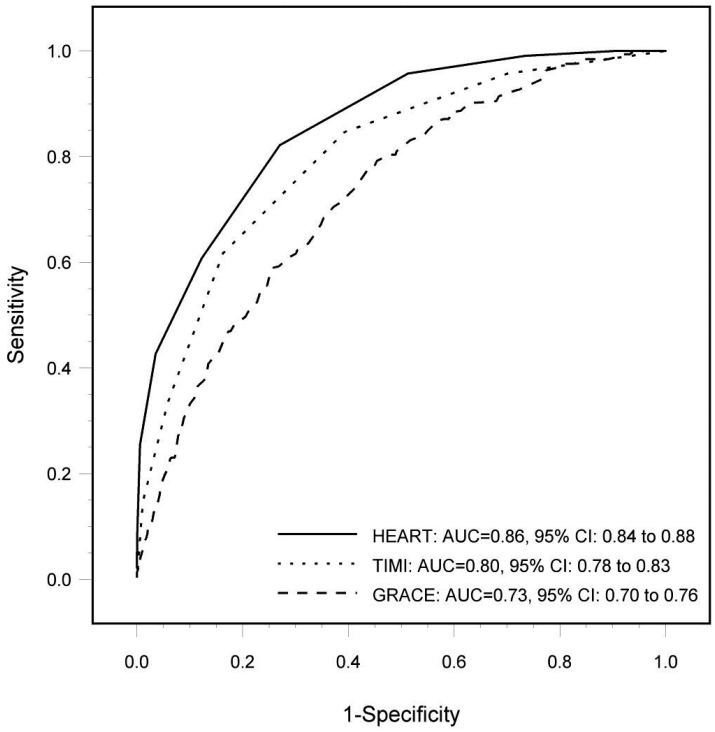
MACE: major adverse cardiac events, AMI: acute myocardial infarction
* at the lowest TIMI score, this absolute safety level is not fulfilled

Table 4. Comparison of performance of GRACE score, HEART score and TIMI score in terms of safety and efficiency, based on the first and second troponin measurement (when performed)

<5.0% patients identified with MACE of total patients with MACE	**GRACE score**	**HEART score**	**TIMI score**
Corresponding cut-off for "low risk"	≤73 points	≤3 points	0 points
Actual number of patients with MACE in "low risk" group / total patients with MACE	14/326 (4.3%)	13/326 (4.0%)	8/326 (2.5%)
Of which AMI	5	3	0
Of which death	0	1	0
Number of patients classified as "low risk" / total number of patients	340/1748 (19.5%)	707/1748 (40.5%)	430/1748 (24.6%)
Percentage of MACE in "low risk" group	4.1% (14/340)	1.8% (13/707)	1.9% (8/430)
<2.0% patients identified with MACE of total patients with MACE	**GRACE score**	**HEART score**	**TIMI score**
Corresponding cut-off for "low risk"	≤67 points	≤2 points	-*
Actual number of patients with MACE in "low risk" group / total patients with MACE	6/326 (1.8%)	3/326 (0.9%)	-
Of which AMI	1	1	-
Of which death	0	0	-
Number of patients classified as "low risk" / total number of patients	243/1748 (13.9%)	381/1748 (21.8%)	-
Percentage of MACE in "low risk" group	2.5% (6/243)	0.8% (3/381)	-

MACE: major adverse cardiac events, AMI: acute myocardial infarction
* at the lowest TIMI score, this absolute safety level is not fulfilled

Figure 2. Receiver-operating-characteristic (ROC) curves and corresponding Areas under the curve (AUCs) of GRACE, HEART and TIMI score to predict major adverse cardiac events within 6 weeks



DISCUSSION

Our head-to-head comparison of three well-known and extensively validated risk scores in 1,748 patients presenting with chest pain at the ED, showed that the HEART score had the highest overall discrimination to predict MACE with an area under the ROC curve of 0.86 (95% CI: 0.84-0.88), followed by the TIMI score with an AUC of 0.80 (95% CI: 0.78-0.83) and the GRACE score (0.73, 95% CI: 0.70-0.76). At a fixed absolute level to define safety the number of low-risk patients identified was higher in HEART (40.5%) than in the GRACE (19.5%) and TIMI scores (24.6%).

In the literature, comparable results were found when comparing the HEART and TIMI scores. In one study, the AUC of the HEART score was 0.83 (95% CI: 0.81-0.85) and the AUC of the TIMI score (0.75, 95% CI: 0.72-0.77) was slightly lower than the AUC of 0.80 we found[22]. In one other study, the GRACE and TIMI risk scores were compared. The TIMI score AUC was 0.79 (95% CI: 0.74–0.83), a similar result we found in our analysis. The AUC

for the GRACE score was considerably higher, namely 0.83 (95% CI: 0.79–0.87), which may possibly be explained by the smaller definition of MACE and shorter duration of follow-up[23]. One valuable role for cardiac risk scores is to identify patients as low-risk in order to avoid further testing and hospital admission in these patients (triage role). An ideal triage instrument would identify the largest number of patients at low risk (i.e. efficiency) without compromising safety, meaning that the number of patients classified as low risk but developing MACE (i.e. false negatives) should be low. When setting an absolute safety level for missed MACE of 5% of total patients, the HEART score identifies the most patients as "low risk", namely 708 patients, with 14 patients missed of the total 326 patients with MACE. This corresponds to a proportion of MACE in the low-risk group of 2.0%. Although the definition of an acceptable false-negative rate is susceptible to personal opinions, and may vary between countries, Than et al. and Kline et al. estimate that the most clinicians would accept a false-negative rate of 1 to 2%[27,28]. When repeating the analyses at a different absolute safety level of missing no more than 2% of all patients with MACE, the HEART score was again the most efficient score with 381 patients identified as low risk, resulting in a cumulative incidence of MACE in this low-risk group of 0.9%; clearly below the mentioned more conservative 1% false-negative rate.

The better performance of the HEART score compared to the TIMI and GRACE scores may be explained by the differences in the patient populations in which the three risk scores were developed. The HEART score was specifically developed for unselected patients with chest pain presenting at the ED, thus, a clinical domain characterized by diagnostic uncertainty[15]. The GRACE score was developed in patients already diagnosed with ACS[29,30]. These patients will have a higher risk of AMI and/or death than an unselected population with chest pain at the ED. The score essentially predicts the short-term prognosis of these patients and may therefore perform worse in predicting the presence of ACS. Similarly, the TIMI score was developed in a group of patients already diagnosed with UA or NSTEMI[19]. Importantly, our HEART-impact trial cohort consisted only of patients in whom a diagnostic dilemma persisted and patients with STEMI were excluded. The GRACE and TIMI scores are well-known scores and are supported by current clinical guidelines[2,4,10,11], but seem more suitable as a (short-term) prognostic score in patients already diagnosed with ACS. A strength of the GRACE score is that it was derived in a large dataset of 11,389 patients[29,30]. The range of the risk score is very wide (1 to 372), therefore small differences in patient characteristics will result in a specific score for every patient. However, the large range of total score outcomes with the GRACE score demands the use of a computer, making it more difficult to apply at the bedside. The HEART and TIMI score have a smaller range of total scores from 0-10 and 0-7 respectively. The HEART scores' strength is that all variables included in the score are derived from clinical practice which makes it simple to calculate the score at the bedside,

improving applicability for physicians. Interestingly, the HEART score was not developed using mathematical modelling from real-life data, but developed by a cardiologist based on clinical experience and later on validated in clinical databases[15]. A limitation of the HEART score is the subjectivity of the first element, (i.e. whether history taking indicates ACS), although every physician agrees this is a clinically relevant element. Furthermore, the score uses a cut-off of 2% as being "low risk", which can arguably be too high in some countries[27,28]. However, the aim of this study was not to determine an optimal cut-off for the risk scores, as this is subject to debate. The TIMI score has as strength that it is comprised of statistically significant predictors, is derived in a large dataset of 1,957 patients and consists of only 7 clinical elements that can be calculated at the bedside. However, the TIMI score only identifies a small proportion of patients as "low risk" who are eligible for early discharge, making it not the most efficient score for triage.

A number of limitations of our study should be mentioned. Firstly, we chose to validate the GRACE, HEART and TIMI scores, while currently several other risk scores are available[12,14,17,18]. We consulted several experienced cardiologists, who found that most currently available risk scores were not used in daily practice, or that the scores included variables not routinely assessed by clinicians (such as measurement of the biomarker Heart Fatty Acid Binding Protein (HFABP)). Secondly, the GRACE score and TIMI score were not determined by the treating physician at the ED, but calculated retrospectively with the use of collected variables, blinded for the primary endpoints. These variables were defined before the start of the trial and included in our data collection form at the ED, since we decided beforehand to calculate the TIMI and GRACE score in our cohort. Clinicians might take other variables into account when calculating a risk score in daily practice; therefore our calculated total scores may differ from calculation in clinical practice. The HEART score was calculated by physicians when including a patient into the HEART-impact trial, and may reflect clinical practice possibly more accurately than the total GRACE scores and TIMI scores, although the GRACE and TIMI score consist of more objective variables than the HEART score. Although the latter makes it unlikely that the GRACE and TIMI scores in our study are different than the scores that would have been derived in clinical practice, we cannot rule out that in our study the performance of the GRACE and TIMI scores could have been underestimated to some extent. Lastly, we did not include serial troponin measurements in our study, while this is currently the policy in most hospitals. We, however, also performed additional analyses based on available second troponin measurements into the calculation of all three risk scores, with the aim to more closely reflect current clinical practice in these hospitals. It should be noted physicians did not perform second troponin measurements in all patients, but only in the patients of whom they deemed this was necessary. Also in these additional analyses, the HEART score had the highest discriminative power.

In conclusion, from our head-to-head comparison of the GRACE, HEART and TIMI score in a large prospective cohort of chest pain patients presenting to the ED, we conclude that the HEART score performed best in discriminating between those with and without ACS. The HEART score identified the largest number of patients (40.5%) as low risk without compromising safety. We recommend the use of the HEART score in the work-up of patients with chest pain at the ED.

COMPETING INTERESTS

Two authors (BEB and AJS) were involved in the development of the HEART score. The authors declare that they have no other competing interests.

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REFERENCES

1. Niska R, Bhuiya F, Xu J. National hospital ambulatory medical care survey: 2007 emergency department summary. National health statistics reports. 2010; 26: 1-31.
2. Thyegesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. European Heart Journal. 2012; 33: 2551–67.
3. Maroko PR, Kjekshus JK, Sobel BE, Watanabe T, Covell JW, Ross J Jr, et al. Factors influencing infarct size following experimental coronary artery occlusions. Circulation 1971; 43:67-82.
4. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. ESC/EACTS Guidelines on myocardial revascularization. European heart journal. 2014; 35: 2541-2619
5. Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, et al. Testing of Low-Risk Patients Presenting to the Emergency Department With Chest Pain: A Scientific Statement From the American Heart Association. Circulation. 2010; 122: 1756-76.
6. Six AJ, Backus BE, Kingma A, Kaandorp SI. Consumption of diagnostic procedures and other cardiology care in chest pain patients after presentation at the emergency department. Netherlands Heart Journal. 2012; 20: 499–504.
7. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, et al. for the ROMICAT-II Investigators. Coronary CT Angiography versus Standard Evaluation in Acute Chest Pain. New England journal of medicine. 2012; 367(4): 299–308.
8. National Institute for Health and Care Excellence. Chest pain of recent onset Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. [document on the internet] NICE clinical guideline 95. Published March 2010. Available from: http://guidance.nice.org.uk/CG95
9. Cannon CP, Brindis RG, Chaitman BR, Cohen DJ, Cross jr. JT, Drozda jr. JP, et al. 2013 ACCF/AHA Key Data Elements and Definitions for Measuring the Clinical Management and Outcomes of Patients With Acute Coronary Syndromes and Coronary Artery Disease. Journal of the American College of Cardiology. 2013; 61(9): 992-1025.
10. VMS veiligheidsprogramma. Praktijkgids ACS [document on the internet]. Webpage VMS zorg. Published March 2010. Available from: http://www.vmszorg.nl/_page/vms_inline?nodeid=4571&subjectid=6705&configid=6490
11. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2015 Aug 29. pii:ehv320.2015.
12. Hess EP, Knoedler MA, Shah ND, Kline JA, Breslin M, Branda ME, et al. The chest pain choice decision aid; a randomized trial. Circulation: cardiovascular quality and outcomes. 2012;5:1-9.
13. Than M, Flaws D, Sanders S, Doust J, Glasziou P, Kline J, et al. Development and validation of the emergency department assessment of chest pain score and 2 h accelerated diagnostic protocol. Emergency Medicine Australasia. 2014; 26(1): 34-44.
14. Lagerqvist B, Diderholm E, Lindahl B, Husted S, Kontny F, Stahle E, et al. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Heart. 2005; 91: 1047–52.
15. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Netherlands Heart Journal. 2008; 16 (6): 191-6.
16. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. The GRACE investigators. Predictors of hospital mortality in the global registry of acute coronary events. Archives of internal medicine. 2003; 163: 2345-53.
17. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook G, et al. The Manchester acute coronary syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. Heart. 2014; 100(18): 1462-8.

18. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation; Results from an international trial of 9461 patients. Circulation. 2000; 101: 2557-67.

19. Antman EM, Cohen M, Bernink PJLM, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI; a method for prognostication and therapeutic decision making. JAMA. 2000; 284: 835-42.

20. Christenson J, Innes G, McKnight D, Thompson CR, Wong H, Yu E, et al. A clinical prediction rule for early discharge of patients with chest pain. Annals of emergency medicine. 2006; 47: 1-10.

21. Mahler SA, Miller CD, Hollander JE, Nagurney JT, Birkhahn R, Singer AJ, et al. Identifying patients for early discharge: performance of decision rules among patients with acute chest pain. International journal of cardiology. 2013; 168(2): 795-802.

22. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART score for the assessment of patients with chest pain in the emergency department. Critical pathways in cardiology. 2013; 12:121-126.

23. Cullen L, Greenslade J, Hammett CJ, Brown AFT, Chew DP, Bilesky J, et al. Comparison of three risk stratification rules for predicting patients with acute coronary syndrome presenting to an Australian emergency department. Heart, Lung and Circulation. 2013; 22: 844-51.

24. Ramsay G, Podogrodzka M, McClure C, Fox Kaa. Risk prediction in patients with suspected cardiac pain: the GRACE and TIMI risk scores versus clinical evaluation. QJM: an international journal of medicine. 2007; 100: 11-18.

25. Poldervaart JM, Reitsma JB, Koffijberg H, Backus BE, Six AJ, Doevendans PA, et al. The impact of the HEART risk score in the early assessment of patients with acute chest pain: design of a stepped wedge, cluster randomised trial. BMC Cardiovascular Disorders. 2013; 13: 77.

26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. Biometrics, 44, 837–845.

27. Than M, Herbert M, Flaws D, Cullen L, Hess E, Hollander JE, et al. What is an acceptible risk for major adverse cardiac event in chest pain patients soon after discharge from the emergency department? International journal of Cardiology. 2013; 166(3): 752-4.

28. Kline JA, Johnson CL, Pollack Jr CV, Diercks DB, Hollander JE, Newgard CD, et al. Pretest probability assessment derived from attribute matching. BMC Med Inform Decis Mak 2005;5:26.

29. Fox Kaa, Eagle KA, Gore JM, Steg PhG, Anderson FA. The GRACe investigators. The global registry of acute coronary events, 1999 to 2009-GRACE. HEART. 2010; 96: 1095-1101.

30. The GRACE investigators. Rationale and design of the GRACE (Global Registry of Acute Coronary Events) Project: A multinational registry of patients hospitalized with acute coronary syndromes. American heart journal. 2001; 141(2): 190-9.

Appendix 1. Information on derivation and validation of the GRACE score, HEART score and TIMI score

GRACE SCORE

The GRACE score was derived in 2003 with a multivariable logistic regression model using 11,389 patients, to stratify risk in patients with ACS at risk for death during hospitalization. (19) The final GRACE score includes Killip classification, systolic blood pressure, heart rate, age, creatinine level, cardiac arrest at admission, ST-segment deviation and elevated cardiac enzyme levels. "Killip class" for congestive heart failure is an increasing scale and contains 4 categories: [1] no signs of congestive heart failure, [2] rales and/or jugular venous distention, [3] pulmonary edema and [4] cardiogenic shock. (30) "Systolic blood pressure" and "heart rate" were measured in mmHg and beats/min respectively. "Age" included patients from 18 years old. "Creatinine level" was measured in mg/dL and blood was collected at admission. "Cardiac arrest at admission" was reported by the physician. "ST segment deviation" was scored if there was ST segment elevation or depression in anterior, inferior or lateral lead groups and was at least 1mm. "Elevated cardiac enzyme levels" were defined as positive troponin I or T, creatinine kinase-MB fraction or creatinine phosphokinase more than 2 times above the upper limit. (19, 31) The total score is calculated by the sum of the corresponding points for each variable. The total score ranges from 1 to 372 points. The GRACE score is calculated by a computer. An calculator can be found at http://www.gracescore.org/. The total GRACE score predicts the probability of in-hospital death.

TIMI SCORE

The TIMI score was derived in 2000 to stratify risk for patients with UA or NSTEMI at risk for the composite endpoint (including AMI, PCI, CABG, and death plus a combined endpoint of AMI, PCI, CABG and death) within 14 days. (22) Another TIMI score was developed for patients with STEMI, but will not be discussed here. (33) To calculate statistical significance of variables, univariate and multivariate logistic regression analysis were performed. The final model of the TIMI score incorporates age, risk factors, significant coronary stenosis, ST deviation, severe anginal symptoms, use of aspirin and elevated cardiac markers. Age is divided in above and below 65 years. Risk factors include family history of coronary artery disease, hypertension, hypercholesterolemia, diabetes or being a current smoker. Significant coronary stenosis is defined as prior coronary stenosis of ≥50%. ST deviation is scored when either transient ST elevation or persistent ST depression of ≥0.01mV is reported. Severe anginal symptoms were defined as more than or equal to 2 events in the last 24 hours. Use

of aspirin must be at least for the last 7 days and elevated serum cardiac markers included creatinine kinase MB fraction and/or troponin level. (22) When a variable is present, the patient receives one point. This results in a score of 0 to 7. The TIMI score provides a percentage of risk for the combined endpoint at the corresponding total score.

HEART SCORE

The HEART score is derived in 2008 and stratifies risk for chest pain patients at the ED at risk for MACE (including AMI, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) and death) within 3 months. (18) HEART score consist of History, ECG, Age, Risk factors and Troponin. "History" is defined as physician's opinion of suspiciousness for ACS from history taking (anamnesis). "ECG" is scored on ST depression, pacemaker rhythm, bundle branch block, repolarization abnormalities or normal ECG. "Age" includes every age above 18 years old. "Risk factors" incorporates history of cardiovascular disease (coronary revascularization, AMI, stroke or peripheral arterial disease), currently treated diabetes mellitus, diagnosed or treated hypertension, diagnosed hypercholesterolemia, current or recent (<3 months) smoker, family history of cardiovascular disease and obesity (body mass index >30). "Troponin" can consist of troponin I, troponin T or high sensitive Troponin and is scored on being below the normal limit, 1 to 3 times the normal limit, or more than 3 times above the normal limit. (18, 24). For each of the variables a score of 0, 1 or 2 points can be given, depending on the severity of the variable, which results in a score of 0 to 10 points. The total score corresponds to an advice for the physician: discharge, further diagnostic testing or (invasive) treatment.

Appendix 2. The GRACE, HEART and TIMI score

(a) The GRACE score

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

3. Look Up Risk Corresponding to Total Points:

Total Points	≤60	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	≥250
Probability of In-Hospital Death, %	≤0.2	0.3	0.4	0.6	0.8	1.1	1.6	2.1	2.9	3.9	5.4	7.3	9.8	13	18	23	29	36	44	≥52

Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163(19):2345-53.

(b) the HEART score

HEART score for chest pain patients

History (Anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-deviation	2	
	Non-specific repolarisation disturbance / LBBB / PM	1	
	Normal	0	
Age	≥ 65 years	2	
	45 – 65 years	1	
	≤ 45 years	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	

HEART

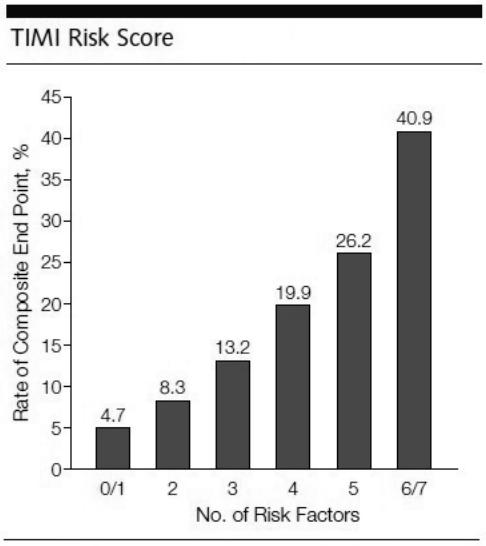
Risk factors for atherosclerotic disease:

Hypercholesterolemia	Cigarette smoking
Hypertension	Positive family history
Diabetes Mellitus	Obesity (BMI>30)

HEART score	Percentage patiënts	Percentage MACE	Proposal for strategy
0-3	32%	1,6%	Discharge (possibly with troponin test at home)
4-6	51%	13%	Observation, non-invasive testing
7-10	17%	50%	Observation, treatment, coronary angiography

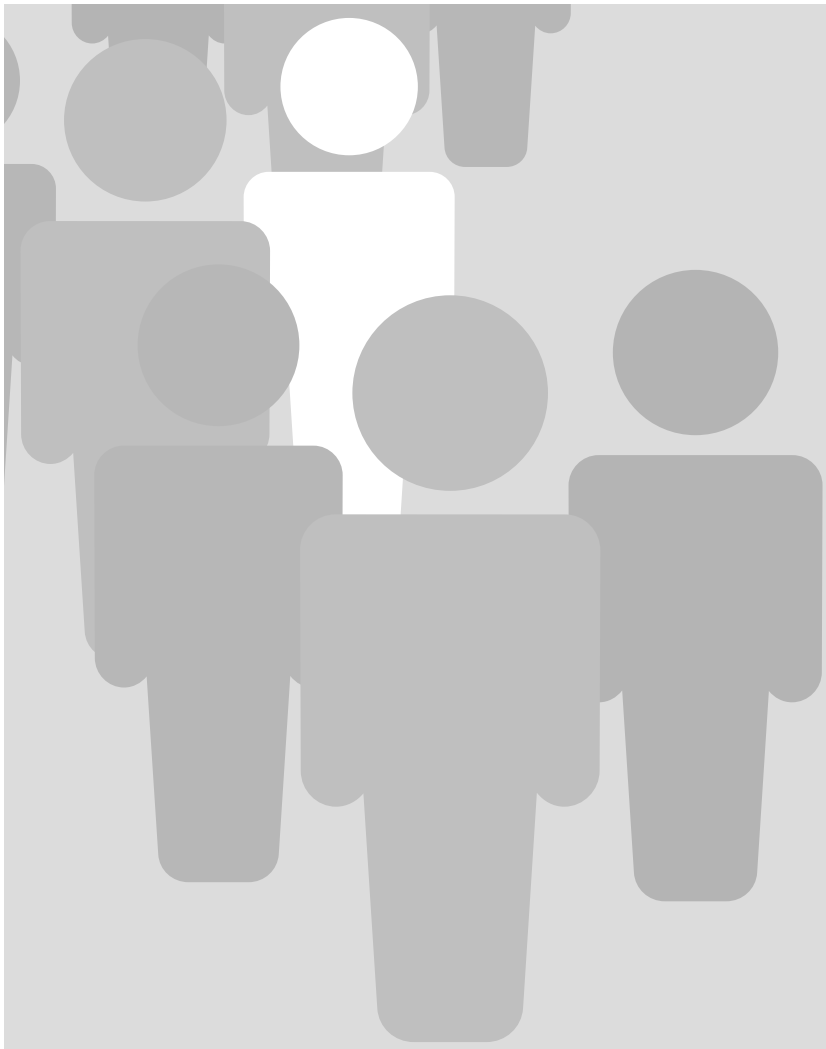
Source: Six AJ., Backus, BE., Kelder JC. Chest pain in the emergency room: value of the HEART score. Netherlands Heart Journal. 2008; 16 (6): 191-6.

(c) the TIMI score



Risk factors
Age, ≥65 years
At least 3 risk factors for coronary artery disease
Significant prior coronary stenosis (≥50%)
ST deviation
Severe angina (≥2 events in the last 24 hours)
Use of aspirin in the last 7 days
Elevated serum cardiac markers

Source: Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000;284(7):835-42.



No added value of novel biomarkers in the diagnostic assessment of patients suspected of acute coronary syndrome

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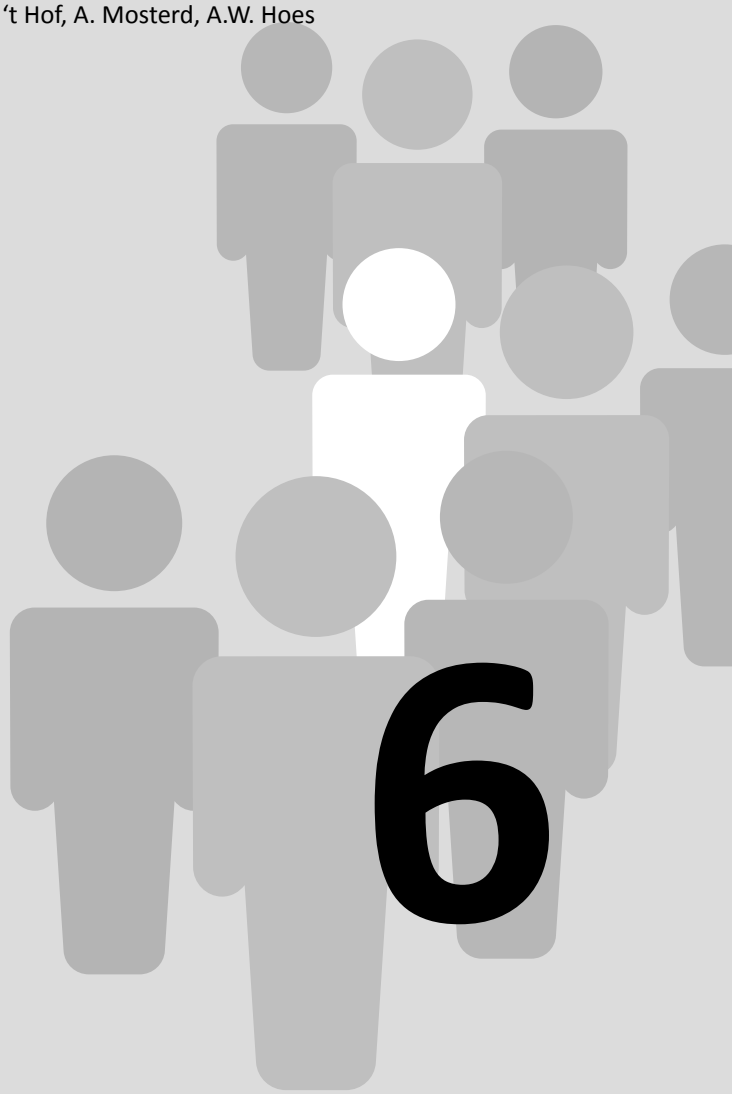

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ABSTRACT

Background: Despite the availability of high-sensitive troponin (hs-cTnT), there is still room for improvement in the diagnostic assessment of patients suspected of acute coronary syndrome (ACS). Apart from serial biomarker testing, which is time-consuming, novel biomarkers like copeptin have been proposed to expedite the early diagnosis of suspected ACS in addition to hs-cTnT. We determined whether placenta derived growth factor (PlGF), soluble Fms-like tyrosine kinase 1 (sFlt-1), myoglobin, N-terminal prohormone B-type Natriuretic Peptide (NT-proBNP), growth-differentiation factor 15 (GDF-15) and copeptin improved early assessment of chest pain patients.

Methods: This prospective, single centre diagnostic FAME-ER study included patients presenting to the ED with symptoms suggestive of ACS. Blood was collected to measure biomarkers, notably, hs-cTnT was retrospectively assessed. Added value of markers was judged by increase in AUC using multivariable logistic regression.

Results: Of 453 patients enrolled, 149 (33%) received a final diagnosis of ACS. Hs-cTnT had the highest diagnostic value in both univariable and multivariable analysis. PPVs of the biomarkers ranged from 23.5% (PlGF) to 77.9% (hs-cTnT), NPVs from 67.0% (PlGF) to 86.4% (hs-cTnT). Only myoglobin yielded diagnostic value in addition to clinical symptoms and electrocardiography (ECG) (AUC of clinical model 0.80) with AUC of 0.84 ($p<0.001$). However, addition of hs-cTnT was superior (AUC 0.89, $p<0.001$). Addition of the biomarkers to our clinical model and hs-cTnT did not or only marginally (GDF-15) improve diagnostic performance.

Conclusion: When assessing patients suspected of ACS, only myoglobin had added diagnostic value beyond clinical symptoms and ECG. However, when combined with hs-cTnT, it yields no additional diagnostic value. PlGF, sFlt-1, NT-proBNP, GDF-15 and copeptin had no added value to the clinical model or hs-cTnT.

BACKGROUND

The diagnostic assessment of patients suspected of acute coronary syndrome (ACS) remains a challenge. In this diagnostic process, biomarkers play a pivotal role when the electrocardiogram (ECG) is inconclusive. Early diagnosis of ACS is essential because of clear improvement in prognosis following timely interventions, while early ruling out of ACS reduces patient burden and costs. Currently, the definitive diagnosis of ACS is based on elevation of high-sensitive cardiac troponin I or T (hs-cTnI or hs-cTnT), in the context of clinical findings and ECG changes[1-4]. Although high sensitive troponin assays can detect circulating troponins at a lower level in the blood than the previous conventional troponin assays, their diagnostic accuracy is still not considered optimal. To further reduce the number of false-positives and false-negatives, serial testing (usually after three hours) has been suggested, but this is time-consuming and increases health care costs[5,6]. Alternatively, other biomarkers, some capable of detecting ischemia very soon after symptom onset, have been proposed to be combined with hs-cTn, for example copeptin, which has been advocated in numerous articles[7-9]. Growth differentiation factor-15 (GDF-15) and copeptin are both markers of stress, the former of hemodynamic and the latter of endogenous stress, and are therefore thought to increase even before necrosis occurs[10,11]. Soluble fms-like tyrosine kinase-1 (sFlt-1) binds placental growth factor (PlGF), a protein that appears to promote the inflammatory process of atherosclerosis and appears to be an early marker of ischemic events[12]. N-terminal prohormone B-type Natriuretic Peptide (NT-proBNP) is a biomarker of myocardial dysfunction and as such reflects the extent of an ischemic insult and its levels correlate with (left) ventricular dysfunction[13,14]. In addition, we also assessed the diagnostic value of myoglobin, a marker of myocardial necrosis, and known for its rapid rise (<2 hours), but its diagnostic value in combination with hs-cTn has not been fully quantified[15]. Importantly, earlier studies on novel biomarkers mostly focus on the diagnostic characteristics of the biomarker per se, rather than assessing the *added* value of the novel biomarkers to readily available information from medical history, clinical signs and symptoms, and ECG[16]. Moreover, the majority of previous studies evaluated novel biomarkers in both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) patients[17,18], while there seems to be no diagnostic dilemma in STEMI patients. The available studies in NSTEMI patients[13,19], where additional biomarkers are more urgently needed, exclude patients with unstable angina (UA), while these patients per definition have non-elevated troponins[1]. Since these patients are at increased risk of cardiovascular events or death, novel biomarkers might be very useful to identify these patients. Our aim was to determine whether the novel biomarkers PlGF, sFlt-1, NT-proBNP, GDF-15 and copeptin, as well as myoglobin improve the early diagnosis or exclusion of myocardial infarction or unstable angina, in patients presenting with chest pain

at the emergency department (ED), in addition to readily available information from patient characteristics, ECG and hs-cTnT.

METHODS

Setting and study population

The FAME-ER (Fatty Acid binding protein in Myocardial infarction Evaluation in the Emergency Room) study was a single centre, prospective diagnostic study among patients presenting to the ED with symptoms suggestive of ACS. After a training period of all professionals involved, all cardiac patients admitted to the ED of the Meander Medical Centre (large regional teaching hospital in Amersfoort, the Netherlands) between May 2007 and November 2007 were identified. Eligible patients were those presenting with symptoms suggestive of ACS within 24 hours of symptom onset. Clear cut ST-segment elevation ACS was an exclusion criterion as these patients underwent primary percutaneous coronary intervention (PCI) elsewhere. Patients of whom no signed informed consent was obtained were excluded. This study complies with the Declaration of Helsinki, furthermore the protocol was approved by the local ethics committee of the Meander Medical Centre.

Routine clinical assessment

Directly upon presentation to the ED, a standard 12-lead ECG was recorded and venous blood was drawn to determine hs-cTnT, the five novel biomarkers and myoglobin. The plasma component was frozen and stored at -70°C until sample analysis. History taking and physical examination was performed by the ED physician or attending cardiologist. All ECGs were interpreted by the attending cardiologist. Patients were diagnosed and treated according to routine clinical protocols (based on European Society of Cardiology (ESC) guidelines)[1,2], including serial ECGs, and measurement of (high sensitive) troponin.

Measurement of biomarkers

For information on biomarker assays and cut-off values, we refer to Appendix 1.

Outcomes

The primary outcome of this study was ACS (i.e. STEMI, NSTEMI and UA). The presence of ACS was determined according to the universal definition of myocardial infarction[3,4] that prevailed at the time of inclusion of participants. A myocardial infarction was defined in accordance with existing guidelines, based on a combination of ischemic symptoms, release of biomarkers of myocardial necrosis (i.e. troponin); with either persistent ST-elevation (STEMI) or no ST-elevation on ECG (NSTEMI)[2,3,4]. Unstable angina was defined as symptoms

associated with dynamic ischemic ECG changes, evidence of ischemia on functional testing or new coronary angiographic changes, without elevation of cTnT. The final diagnosis was made during consensus meetings of an outcome panel (two cardiologists, one resident). The final diagnosis was based on all available clinical information including serial conventional cTnI measurements, a single hs-cTnT measurement, serial ECG findings and hospital discharge letters. Determination of a single hs-cTnT measurement was performed post hoc from the frozen plasma. The outcome panel was blinded to results of the novel biomarkers to prevent incorporation bias[20].

Statistical analysis

Continuous variables are presented as means (± standard deviation, SD) or medians (interquartile range, IQR), while categorical variables are presented as numbers (percentage). Comparisons of continuous variables were made with the use of the Mann-Whitney *U*-test. From 2x2 tables, the sensitivity, specificity, and predictive values were calculated. The cut-off values of the biomarkers PlGF (27pg/ml), sFlt-1 (70pg/ml), myoglobin (50ng/ml), NT-proBNP (125pg/ml), GDF-15 (1800pg/ml), and copeptin (14pmol/l) were based on the available literature[9,10,13,18,21-23]. Receiver operating characteristic (ROC) curves were created and the area under the curve (AUC) was calculated to quantify the diagnostic accuracy of each individual biomarker. Odds ratios (OR) of all possible predictors of ACS were calculated by univariable logistic regression. These predictors were selected based on the literature and clinical experience. From these predictors a clinical model was developed (in part based on their availability at presentation) using the following predictors: patient history (age, sex, previous myocardial infarction, PCI or coronary artery bypass graft (CABG)), cardiovascular risk factors (hypertension, hypercholesterolemia, family history of cardiovascular disease (CVD), smoking, diabetes mellitus) and ECG findings. The diagnostic value of the novel biomarkers in addition to the clinical model, as well as of the clinical model alone, was estimated by using multivariable regression, likelihood ratio's and ROC curves analyses including the biomarkers as continuous variables[24]. Because of skewed distribution (and linearity) all biomarkers were transformed using natural logarithm. Restricted cubic splines were used to test whether continuous variables had a linear association with the outcome. Discrimination of the multivariable models was determined by the AUC or c-statistic indicating the probability that two patients (one with and one without ACS) are classified correctly[24]. Bootstrapping techniques were used as a validation method to adjust for over-optimism[25]. We performed additional analyses to study whether the diagnostic accuracy differed according to time since onset of symptoms (<3 hours). Multiple imputation techniques were applied in case of missing values[26]. We followed the STARD (Standards for reporting of diagnostic accuracy) checklist[27,28]. All analyses were performed using Statistical Package for the Social Sciences for Windows 20.0 (SPSS Incl. Chicago, Illinois).

RESULTS

Patient characteristics

A total of 1,110 patients with symptoms suggestive of ACS were identified. Of these, 567 patients were excluded due to time constraints or no obtained informed consent. Another 90 patients were excluded because of major missing values (outcome, hs-cTnT measurements) and/or symptom onset unknown or >24 hours. Eventually, 453 patients were enrolled (Figure 1). Baseline characteristics are shown in Table 1. Mean age was 62.7 years and 56% was male. Median time between onset of symptoms and presentation at the ED was 3.0 hours. ACS was diagnosed in 149 (33%) patients: 13 (3%) STEMI, 104 (23%) NSTEMI, and 32 (7%) UA. The non-ACS group consisted of 304 individuals with a final diagnosis of stable angina (n=48), rhythm disorders (n=14), heart failure (n=4), pericarditis (n=1) or non-cardiac diagnoses (n=237; e.g. aspecific chest pain, gastroesophageal reflux disease, myalgic chest pain). Patients who presented at the ED within three hours, were similar to the overall group, except for smoking, history of MI, PCI or CABG, and hypertension. In these patients, ACS was diagnosed in 67 (34%) cases. The completeness of the data for each biomarker is as follows: hs-cTnT 100%, PlGF 99.8%, sFlt-1 99.1%, myoglobin 100%, NT-proBNP 99.8%, GDF-15 99.8%, copeptin 68.2%.

Figure 1. Flow chart of patient selection from all patients with symptoms suggestive of ACS to enrolled patients

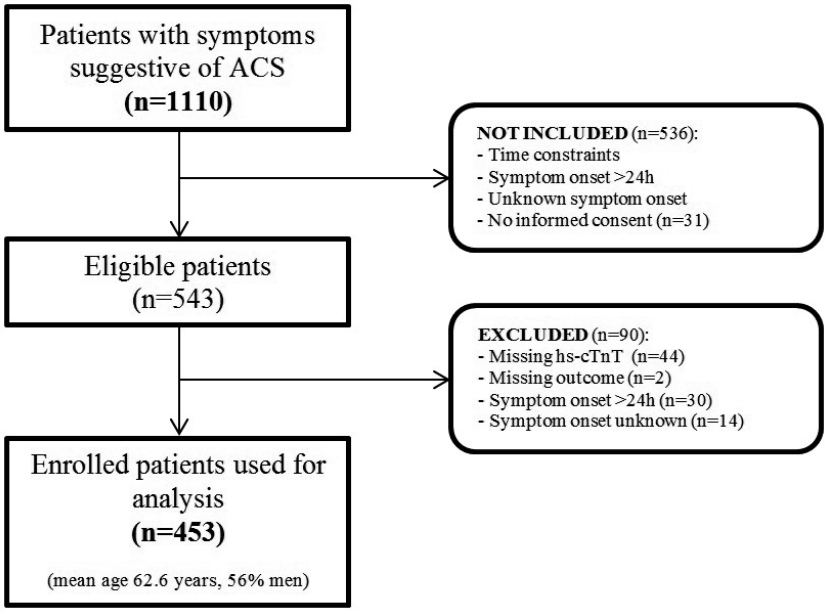

Table 1. Baseline characteristics stratified by time of presentation after symptom onset

Characteristics	N	All patients	N	Patients within 3h of symptom onset (n=197)
Age, mean years	453	62.6 ± 14.5	197	61.8 ± 15.1
Male gender	453	253 (56%)	197	108 (55%)
Duration of symptoms in hours, median (IQR)	430	3.0 (1.8-6.8)	197	1.6 (1.2-2.2)
Hypertension	447	193 (43%)	194	68 (35%)
Hypercholesterolemia	447	148 (33%)	194	63 (33%)
Diabetes mellitus	447	72 (16%)	193	27 (14%)
Current smoker	444	114 (26%)	192	58 (30%)
Former smoker	444	111 (25%)	192	51 (27%)
Family history of CVD	442	181 (41%)	190	75 (40%)
BMI, mean kg/m²	320	27.0 ± 4.7	139	26.5 ± 4.5
Previous CVA	447	7 (2%)	194	3 (2%)
Previous TIA	447	22 (5%)	194	7 (4%)
Previous MI	446	96 (22%)	193	50 (26%)
Previous PCI	447	97 (22%)	194	48 (25%)
Previous CABG	446	45 (10%)	193	19 (10%)
Any MI, PCI or CABG	450	150 (33%)	196	73 (37%)
Heart failure	448	24 (5%)	194	12 (6%)
Peripheral arterial disease	447	25 (6%)	194	14 (7%)
Current aspirin use	440	187 (43%)	192	84 (44%)
Current clopidogrel use	436	50 (12%)	190	23 (12%)
Current coumarin use	436	47 (11%)	190	18 (10%)
Current ß-blocker use	437	171 (39%)	191	75 (39%)
Current statin use	439	176 (40%)	131	83 (44%)
Outcome of ACS	453	149 (33%)	197	67 (34%)
- STEMI		13 (3%)		7 (4%)
- NSTEMI		104 (23%)		43 (22%)
- UA		32 (7%)		17 (9%)

Values are given as mean (±Standard Deviation), median (IQR=Inter Quartile Range) or proportion (%)
CVD: cardiovascular disease, BMI: body mass index, CVA: cerebrovascular accident, TIA: transient ischemic attack, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft

Univariable analysis

Median levels of hs-cTnT, PlGF, sFlt-1, myoglobin, NT-proBNP, GDF-15 and copeptin were higher in ACS patients than in non-ACS patients (Table 2). Hs-cTnT had the largest AUC (0.86, 95% confidence interval (CI) 0.81-0.91) (Table 3). Myoglobin and NT-proBNP each had an AUC of 0.75 (95% CI: 0.69-0.81), while the AUCs for PlGF, sFlt-1, GDF-15 and copeptin were lower. Of all biomarkers, hs-cTnT had both the highest positive predictive value (PPV) and negative predictive value (NPV): 77.9% and 86.4% respectively (Table 3). Also in the group of patients presenting within three hours, hs-cTnT still had the highest PPV and NPV (Table 4). On average, the PPVs increased and the NPVs decreased compared to the overall group.

Strong clinical predictors for the presence of ACS were age (OR 1.05 per year), male gender (OR 1.63), a history of hypertension (OR 2.24), hypercholesterolemia (OR 1.71) or heart failure (OR 3.99), MI on ECG (OR 5.31) or ischemic ECG (OR 7.87) and the use of aspirin (OR 1.70), clopidogrel (OR 2.53) and β-blocker (OR 1.84) (Table 5).

Table 2. Median biomarker concentrations and inter quartile ranges stratified by ACS status

Marker	ACS		p-value
	Yes n=149	No n=304	
hs-cTnT (pg/mL)	25.2 (11.7-81.1)	3.3 (1.2-7.7)	<0.001
PlGF (pg/mL)	17.3 (13.6-20.0)	14.0 (11.2-17.1)	<0.001
sFlt-1 (pg/mL)	69.7 (61.4-79.5)	63.3 (55.6-72.2)	<0.001
Myoglobin (ng/mL)	56.2 (40.2-121.4)	37.1 (29.1-48.8)	<0.001
NT-proBNP (pg/mL)	330.3 (118.8-1245.8)	78.8 (30.7-207.6)	<0.001
GDF-15 (pg/mL)	1221.0 (914.1-2160.7)	884.3 (672.5-1307.4)	<0.001
Copeptin (pmol/L)	9.2 (1.0-29.5)	6.2 (1.0-14.1)	0.005

Values are given as median (Inter Quartile Range); p-value calculated with Mann-Whitney *U*-test
hs-cTnT: high-sensitive cardiac troponin, PlGF: placental growth factor, sFlt-1: soluble Fms-like tyrosine kinase-1, NT-proBNP: N-terminal prohormone B-type Natriuretic Peptide, GDF-15: growth differentiation factor-15

Table 3. Sensitivity, specificity, predictive values and AUCs of hs-cTnT, myoglobin and 5 novel biomarkers in all patients

	All patients (n=453)				
Marker	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**AUC**
hs-cTnT	71.1% (63.8-78.4)	90.1% (86.8-93.5)	77.9% (71.0-84.9)	86.4% (82.7-90.2)	0.86 (0.81-0.91)
PlGF	2.7% (0.1-5.3)	95.7% (93.4-98.0)	23.5% (3.4-43.7)	67.0% (62.5-71.3)	0.68 (0.62-0.74)
sFlt-1	47.3% (39.2-55.4)	72.3% (67.2-77.3)	45.1% (37.2-53.0)	74.0% (69.0-79.0)	0.62 (0.56-0.69)
Myoglobin	59.7% (51.9-67.6)	76.3% (71.5-81.1)	55.3% (47.6-63.0)	79.5% (74.8-84.1)	0.75 (0.69-0.81)
NT-proBNP	73.8% (66.8-80.9)	61.4% (55.9-66.9)	48.5% (42.0-55.0)	82.7% (77.7-87.6)	0.73 (0.67-0.79)
GDF-15	34.9% (27.2-42.6)	87.1% (83.4-90.9)	57.1% (47.0-67.3)	73.1% (68.6-77.7)	0.66 (0.59-0.72)
Copeptin	38.6% (29.1-48.1)	75.0% (69.1-80.9)	42.9% (32.7-53.0)	71.6% (65.6-77.5)	0.60 (0.53-0.67)

Values are given as percentage or number (95%CI)
hs-cTnT: high-sensitive cardiac troponin, PlGF: placental growth factor, sFlt-1: soluble Fms-like tyrosine kinase-1, NT-proBNP: N-terminal prohormone B-type Natriuretic Peptide, GDF-15: growth differentiation factor-15, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve

Table 4. Sensitivity, specificity, predictive values and AUCs of hs-cTnT, myoglobin and 5 novel biomarkers in patients with symptom onset within 3 hours

	Patients with symptom onset <3h (n=197)				
Marker	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**AUC**
hs-cTnT	62.7% (51.1-74.3)	92.3% (87.7-96.9)	80.8% (70.1-91.5)	82.8% (76.6-88.9)	0.86 (79.0-92.8)
PlGF	3.0% (0.0-7.1)	97.7% (95.1-100)	40.0% (0.0-82.9)	66.1% (59.5-73.0)	0.71 (62.1-80.2)
sFlt-1	43.3% (31.4-55.1)	77.5% (70.3-84.7)	50.0% (37.1-62.9)	72.5% (65.0-79.9)	0.62 (52.2-71.9)
Myoglobin	55.2% (43.3-67.1)	78.5% (71.4-85.5)	56.9% (44.9-69.0)	77.3% (70.1-84.4)	0.76 (67.0-84.0)
NT-proBNP	68.7% (57.5-79.8)	66.7% (58.5-74.8)	51.7% (41.3-62.1)	80.4% (72.8-87.9)	0.74 (65.1-82.9)
GDF-15	34.3% (23.0-45.7)	89.2% (83.9-94.6)	62.2% (46.5-77.8)	72.5% (65.6-79.4)	0.66 (56.1-76.1)
Copeptin	39.6% (25.7-53.4)	69.4% (59.6-79.2)	42.2% (27.8-56.7)	67.0% (57.2-76.9)	0.57 (46.6-67.4)

Values are given as percentage or number (95%CI)
hs-cTnT: high-sensitive cardiac troponin, PlGF: placental growth factor, sFlt-1: soluble Fms-like tyrosine kinase-1, NT-proBNP: N-terminal prohormone B-type Natriuretic Peptide, GDF-15: growth differentiation factor-15, PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve

Multivariable analysis

The clinical model with age, sex, history of MI, PCI or CABG, cardiovascular risk factors and ECG features resulted in an AUC of 0.80 (Table 6, Figure 2). Addition of hs-cTnT to this model resulted in the most profound increase in the AUC (0.89; Likelihood ratio test (LR test) p<0.001). Only addition of myoglobin to the clinical model showed a small (significant) increase in the AUC of 0.84. Addition of any of the novel biomarkers to the clinical model and hs-cTnT levels did not or only marginally increase the AUC (Table 6; all AUCs 0.88-0.90), although adding GDF-15 (significantly) improved calibration (LR test p=0.026). Combining all the biomarkers with the clinical model did not result in an increase in AUC (0.89). Similar results were observed in patients presenting to the ED <3 hours (Table 7). Adding hs-cTnT to the clinical model resulted in the highest increase in AUC (0.88, LR test p<0.001). None of the other biomarkers yielded diagnostic information in addition to the clinical model and hs-cTnT levels, with the exception of copeptin, which showed an AUC of 0.89 (non-significant).

Table 5. Univariable analysis of possible predictors

	Predictor	ACS n=149	Non-ACS n=304	Odds Ratio	95% CI
Risk factors	Age	69.0±13.2	59.5±14.1	1.05	1.04-1.07
	Male gender	95 (63.8%)	158 (52.0%)	1.63	1.09-2.43
	Hypertension	86 (57.7%)	112 (36.8%)	2.24	1.50-3.36
	Hypercholesterolemia	61 (40.9%)	90 (29.6%)	1.71	1.13-2.59
	Diabetes mellitus	29 (19.5%)	44 (14.5%)	1.46	0.87-2.45
	Current smoker	37 (24.8%)	77 (25.3%)	0.96	0.59-1.57
	Former smoker	38 (25.5%)	81 (26.6%)	0.92	0.57-1.50
	Family history of CVD	67 (45.0%)	121 (39.8%)	1.21	0.81-1.81
History	Previous CVA	6 (4.0%)	5 (1.6%)	2.23	0.57-8.76
	Previous TIA	8 (5.4%)	14 (4.6%)	1.30	0.53-3.21
	Previous MI	45 (30.2%)	55 (18.1%)	1.98	1.25-3.13
	Previous PCI	36 (24.2%)	62 (20.4%)	1.29	0.81-2.06
	Previous CABG	21 (14.1%)	25 (8.2%)	1.80	0.97-3.35
	Any MI, PCI or CABG	64 (43.0%)	87 (28.6%)	1.86	1.24-2.81
	Heart failure	16 (10.7%)	9 (3.0%)	3.99	1.69-9.43
	PAD	15 (10.1%)	14 (4.6%)	2.21	1.00-4.90
Medication	Current aspirin use	76 (51.0%)	115 (37.8%)	1.70	1.14-2.53
	Current clopidogrel use	28 (18.8%)	25 (8.2%)	2.53	1.41-4.54
	Current coumarin use	21 (14.1%)	27 (8.9%)	1.74	0.95-3.18
	Current β-inhibitor use	73 (49.0%)	104 (34.2%)	1.84	1.23-2.75
	Current statin use	66 (44.3%)	112 (36.8%)	1.34	0.89-2.01
ECG	Acute MI on ECG	18 (12.1%)	8 (2.6%)	5.31	0.81-34.84
	Ischemic ECG	103 (69.1%)	66 (21.7%)	7.87	4.96-12.48

Values are given as mean (±SD) or proportion (%)
CVD: cardiovascular disease, CVA: cerebrovascular accident, TIA: transient ischemic attack, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, PAD: peripheral arterial disease, ECG: electrocardiogram, ACS: acute coronary syndrome, CI: confidence interval

Table 6. Multivariable analysis including all patients (n=453)

Model	AUC*	95% CI	Likelihood ratio test (p-value)
Clinical model	0.80	0.76-0.84	
Clinical model with hs-cTnT	0.89	0.87-0.94	p<0.001**
Clinical model with PlGF	0.81	0.77-0.85	p=0.887**
Clinical model with sFlt-1	0.82	0.78-0.86	p=0.001**
Clinical model with myoglobin	0.84	0.80-0.88	p<0.001**
Clinical model with NT-proBNP	0.82	0.79-0.87	p<0.001**
Clinical model with GDF-15	0.81	0.77-0.85	p=0.664**
Clinical model with copeptin	0.81	0.77-0.85	p=0.683**
Clinical model, hs-cTnT and PlGF	0.88	0.86-0.93	p=0.081***
Clinical model, hs-cTnT and sFlt-1	0.88	0.86-0.92	p=0.892***
Clinical model, hs-cTnT and myoglobin	0.88	0.86-0.93	p=0.693***
Clinical model, hs-cTnT and NT-proBNP	0.88	0.86-0.92	p=0.216***
Clinical model, hs-cTnT and GDF-15	0.90	0.87-0.94	p=0.026***
Clinical model, hs-cTnT and copeptin	0.88	0.86-0.92	p=0.315***
Clinical model with *all* biomarkers	0.89	0.87-0.93	p<0.001** p=0.191***

Clinical model: Age, sex, hypertension, hypercholesterolemia, family history of CVD, current and former smoking, diabetes mellitus, and history of MI, PCI or CABG and ECG
hs-cTnT: high-sensitive cardiac troponin, PlGF: placental growth factor, sFlt-1: soluble Fms-like tyrosine kinase-1, NT-proBNP: N-terminal prohormone B-type Natriuretic Peptide, GDF-15: growth differentiation factor-1, AUC: area under the receiver operating curve (ROC), CI: confidence interval
*adjusted for over-optimism; ** compared to the Clinical model; *** compared to the Clinical model + hs-cTnT

Figure 2. Receiver-operating-characteristic curves of the clinical model with the various biomarkers, high sensitive cardiac troponin T (hs-cTnT), placental growth factor (PlGF), fms-like tyrosine kinase-1 (sFlt-1), myoglobin, N-terminal prohormone B-type Natriuretic Peptide (NT-proBNP), growth differentiation factor-15 (GDF-15) and copeptin (ROC curve shown is from the first imputation set)

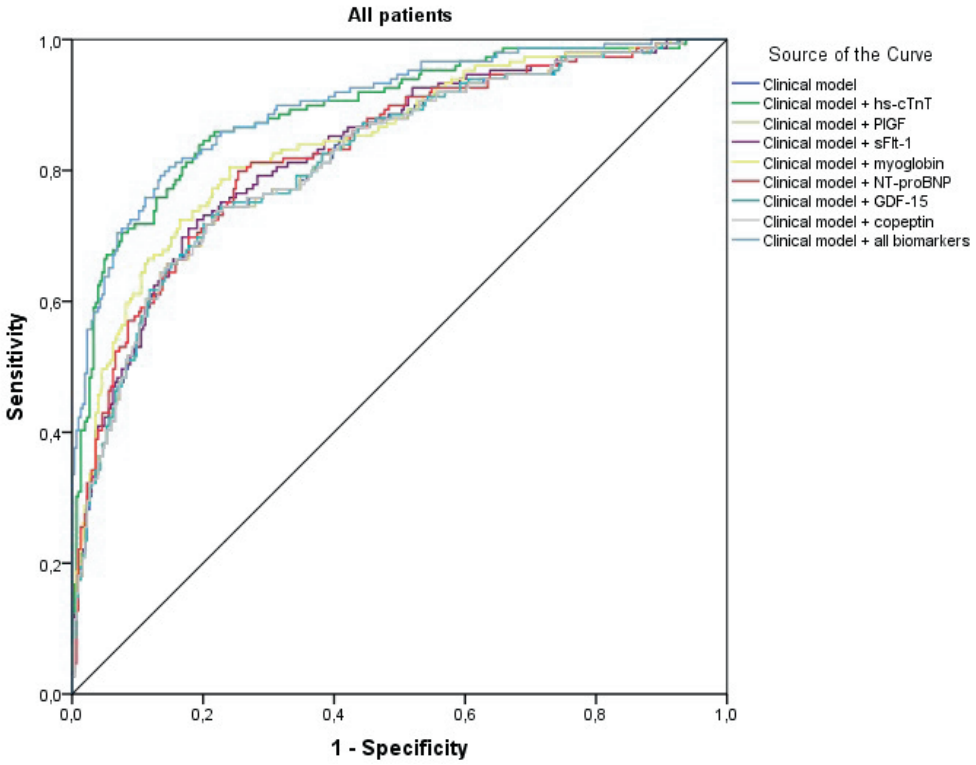

Table 7. Multivariable analysis including patients < 3 hours of symptom onset (n=197)

Model	AUC*	95% CI	Likelihood ratio test (p-value)
Clinical model	0.81	0.75-0.87	
Clinical model with hs-cTnT	0.88	0.84-0.94	p<0.001**
Clinical model with PlGF	0.82	0.76-0.88	p=0.519**
Clinical model with sFlt-1	0.82	0.76-0.88	p=0.068**
Clinical model with myoglobin	0.83	0.77-0.89	p=0.015**
Clinical model with NT-proBNP	0.84	0.78-0.90	p=0.003**
Clinical model with GDF-15	0.82	0.76-0.88	p=0.800**
Clinical model with copeptin	0.82	0.76-0.88	p=0.355**
Clinical model, hs-cTnT and PlGF	0.88	0.85-0.94	p=0.470***
Clinical model, hs-cTnT and sFlt-1	0.87	0.84-0.93	p=0.688***
Clinical model, hs-cTnT and myoglobin	0.88	0.85-0.94	p=0.766***
Clinical model, hs-cTnT and NT-proBNP	0.88	0.84-0.94	p=0.404***
Clinical model, hs-cTnT and GDF-15	0.88	0.85-0.94	p=0.182***
Clinical model, hs-cTnT and copeptin	0.89	0.85-0.94	p=0.169***
Clinical model with *all* biomarkers	0.89	0.85-0.94	p<0.001** p=0.304***

Clinical model: Age, sex, hypertension, hypercholesterolemia, family history of CVD, current and former smoking, diabetes mellitus, and history of MI, PCI or CABG, and ECG
hs-cTnT: high-sensitive cardiac troponin, PlGF: placental growth factor, sFlt-1: soluble Fms-like tyrosine kinase-1, NT-proBNP: N-terminal prohormone B-type Natriuretic Peptide, GDF-15: growth differentiation factor-1, AUC: area under the receiver operating curve (ROC), CI: confidence interval
*adjusted for over-optimism; ** compared to the Clinical model; *** compared to the Clinical model + hs-cTnT

DISCUSSION

In patients suspected of ACS, high-sensitive troponin assays are not always conclusive in the first hours after symptom onset, and so the search for novel early biomarkers is ongoing. This prospective study assessed the diagnostic value of several novel biomarkers in combination with the patient's history, cardiovascular risk factors and ECG findings, in diagnosing ACS at an early stage. Our results show that hs-cTnT is still the best biomarker when trying to determine the presence of ACS, both in a single marker diagnosis and when integrated into our clinical model (AUCs of respective 0.86 and 0.89). The biomarker myoglobin provided additional value to the clinical model, but not when hs-cTnT was added to the clinical model (AUC 0.88). The other biomarkers studied provided no additional diagnostic information to the clinical model.

We compared our results with those from other recent biomarker studies. Firstly, copeptin has been extensively investigated as a possible addition to hs-cTn, with several recent studies presenting promising results. Meune et al. measured hs-cTnT and copeptin in a comparable study population with the same cut-off values for the biomarkers[8]. They found a NPV of 82.6% when combining copeptin with hs-cTnT on admission, and an AUC of 0.94, compared to a NPV of 76.5% and an AUC of 0.90 for hs-cTnT on admission alone (non-significant difference). This apparent advantage of using copeptin is diminished when looking at hs-cTnT values at three hours after admission. They show a NPV of 83.9% and an AUC of 0.94. Maisel et al. showed in a recent large trial that adding copeptin to cTnI allowed safe rule out of AMI with a NPV of 99%, promoting a multimarker approach, whereas our study did not show a significant added value of copeptin[9]. Möckel et al. concluded in a RCT on 902 patients that a single measurement of troponin and copeptin allows for early discharge of low- to intermediate-risk patients with suspected ACS and seems to be safe[29]. However, mentioned studies did not incorporate a clinical model in their studies, making an assessment of the added value of copeptin to clinical characteristics impossible. Furthermore, earlier studies that did find a significant advantage of using copeptin for early diagnosis or exclusion mostly used conventional troponin assays, instead of high sensitive troponin assays, or included patients with STEMIs[17,23]. Secondly, similar to our findings, Schaub et al. showed there is little value in using GDF-15 as a diagnostic test in chest pain patients. GDF-15 seems more valuable as a prognostic marker[10,18]. Thirdly, PlGF and NT-proBNP have also been previously investigated. In a study where both markers are explored in a single marker strategy, PlGF has a sensitivity of 24%, a specificity of 70% and an AUC of 0.50, while the corresponding findings in our study were 2.7%, 95.7% and 0.68 respectively[13]. Although these values differ considerably, both studies concluded that PlGF is not suitable for a single marker strategy. Their results for NT-proBNP also differed from ours, but to a lesser extent. When added to conventional troponin I, PlGF and NT-proBNP did not provide any clinically significant additional diagnostic value in their study; a finding confirmed in our study. Lastly, when comparing hs-cTnT with myoglobin, our results are in line with other studies as well[30].

Half of the studies mentioned above used the standard, non-high-sensitive troponin assays, whereas one of the strengths of our study is the use of a high-sensitive assay. Earlier studies confirmed the higher sensitivity of the so-called high sensitivity troponin assays compared to conventional assays[5,6]. However, higher sensitivity is usually accompanied by lower specificity and concerns have been raised about the number of false-positives[8,19]. Mechanisms other than coronary artery plaque rupture (main cause of type 1 myocardial infarction) can cause myocardial injury and result in elevation of troponin, like heart failure, renal failure and sepsis. These so called type 2 myocardial infarctions result from an imbalance between myocardial oxygen supply and/or demand, other examples of which are coronary vasospasm, anaemia and hypotension[4,13,19,31].

As the search for the perfect biomarker continues, many researchers support a multimarker approach in diagnosing ACS[29,32]. Such an approach is not only advocated to be able to diagnose ACS quickly, but also to find a cause for the elevated troponin levels in other heart diseases and non-cardiac diseases[19]. A multimarker strategy combining cardiac troponin with other markers of myocardial damage, or biomarkers "upstream" from necrosis, may help to gain insight into the pathophysiological mechanisms causing non-ACS related troponin leakage[10].

We aimed to develop such a multimarker strategy with the aid of some biomarkers often advocated as useful adjuncts to hs-cTn, but were unsuccessful. None of these added relevant diagnostic information to a clinical model plus hs-cTnT. Previous studies investigating novel biomarkers predominantly focused on myocardial infarctions as the primary outcome[13,17,19]. However, patients with unstable angina are at a clearly increased risk of adverse cardiovascular events[1,2]. Recognizing these patients early and treating them accordingly is likely to improve prognosis. We therefore chose to include UA in our outcome. Unfortunately, subgroup analyses comparing patients with unstable angina versus "no ACS" revealed no additional value of the novel biomarkers compared with the clinical model alone (AUC of the clinical model 0.79 versus AUC of clinical model with single novel biomarker ranging from 0.76 to 0.79). It should be emphasized, however, that the number of UA patients is small. These findings should therefore be interpreted with caution.

One of the strengths of our study is the manner in which we conducted our data analysis to enable us to quantify the additional value of the biomarkers. We applied multiple imputation in case of missing values, and performed multivariable regression analysis to assess the value of the various biomarkers in combination with a patient's history and ECG. We recognize that our study has several limitations. Firstly, we used panel diagnosis for final adjudication of our outcome. However, in the absence of a reference standard, there is no alternative when one is interested in a clinically relevant outcome, furthermore, expert panels are widely accepted[33,34]. Secondly, we only have single measurements of hs-cTnT, instead of serial measurements. Moreover, these measurements were assessed retrospectively. Thirdly, the completeness of the data for each biomarker was ranging from 99.1-100% in all biomarkers, except for copeptin, with complete data in 68.2%. Because we decided to investigate copeptin after the first analysis of the frozen samples had been done, we had a relative high number of missing values for copeptin, since for a number of participants no frozen samples were available. In our analyses we used multiple imputation to counteract this deficit. Moreover, the availability of remaining blood samples is very likely to be a random phenomenon and unrelated to the patients characteristics or outcome. Fourthly, we used one cut-off value for each biomarker, based on the available literature or clinical grounds. Theoretically, performance of these biomarkers could improve by using

either a lower or higher cut-off value to detect ACS. Sensitivity analyses applying other cut-off points, however, did not improve diagnostic value of the markers. Fifthly, due to the observational nature of our study, we cannot provide any data on the possible effect of the use of these biomarkers on the patients' prognosis, but such an effect is likely to be very limited in view of the minimal diagnostic yield of adding the biomarkers. Lastly, we used our prediction model on both our entire population and on the subgroup of patients presenting within 3 hours. The low number of events in combination with the number of predictors in our model could induce overfitting[35,36].

In conclusion, of the biomarkers tested, only the use of myoglobin had additional value to our clinical model in patients suspected of ACS. However, hs-cTnT was superior to all other biomarkers when used with our clinical model as well as in a single marker strategy and none of the other biomarkers provided significant diagnostic information in addition to the clinical model and hs-cTn. Research on the added value of novel biomarkers to complement troponin and clinical assessment should continue to further limit the number of false-positives and false-negatives.

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REFERENCES

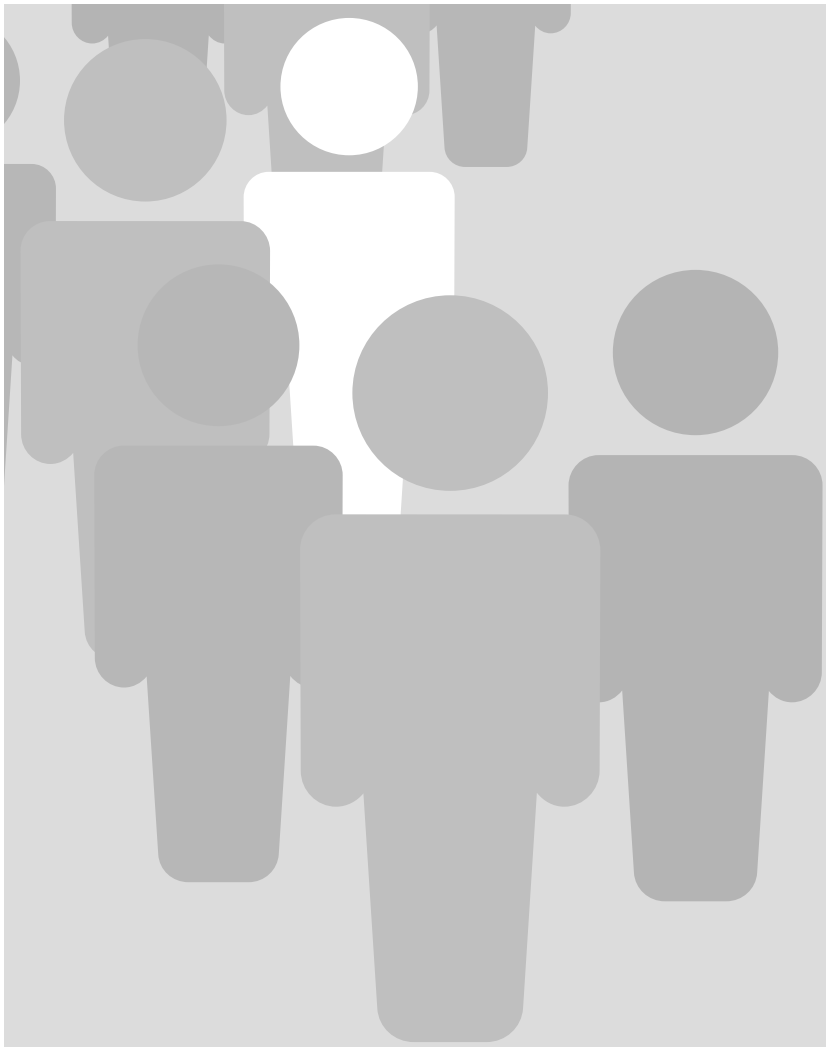
1. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;28(13):1598-1660.
2. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2011 Dec;32(23):2999-3054.
3. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Circulation* 2007;116(22):2634-2653.
4. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012; 60(16):1581-98.
5. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, et al. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med* 2009;361(9):868-877.
6. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med* 2009;361(9):858-867.
7. Bohyn E, Dubie E, Lebrun C, Jund J, Beaune G, Lesage P, et al. Expeditious exclusion of acute coronary syndrome diagnosis by combined measurements of copeptin, high-sensititity troponin, and Grace score. *Am J Emerg Med* 2013;3:829-2
8. Meune C, Zuily S, Wahbi K, Claessens YE, Weber S, Chenevier-Gobeaux C. Combination of copeptin and high-sensititvity cardiac troponin T assay in unstable angina and non-ST-segment elevation myocardial infarction: A pilot study. *Arch Cardiovasc Dis* 2011;104(1):4-10
9. Maisel A, Mueller C, Neath SX, Christenson RH, Morgenthaler NG, McCord J, et al. Copeptin helps in the early detection of patients with acute myocardial infarction: primary results of the CHOPIN trial (Copeptin Helps in the early detection Of Patients with acute myocardial INfarction). *J Am Coll Cardiol.* 2013;62(2):150-60.
10. Eggers KM, Kempf T, Allhoff T, Lindahl B, Wallentin L, Wollert KC. Growth-differentiation factor-15 for early risk stratification in patients with acute chest pain. *Eur Heart J* 2008;2327-2335
11. Morgenthaler NG. Copeptin: a biomarker of cardiovascular and renal function. *Congest Heart Fail* 2010;16:S37-44
12. Hochholzer W, Reichlin T, Stelzig C, Hochholzer K, Meissner J, Breidthardt T, et al. Impact of soluble fms-like tyrosine kinase-1 and placental growth factor serum levels for risk stratification and early diagnosis in patients with suspected acute myocardial infarction. *Eur Heart J* 2011;32: 326-335
13. Apple FS, Smith SW, Pearce LA, Murakami MM. Assessment of the Multiple-Biomarker Approach for Diagnosis of Myocardial Infarction in Patients Presenting with Symptoms Suggestive of Acute Coronary Syndrome. *Clin Chem* 2009;55:93-100
14. Morrow DA, Braunwald E. Future of biomarkers in acute coronary syndromes: moving toward a multimarker strategy. *Circulation* 2003;108:250-2
15. Kehl DW, Iqbal N, Fard A, Kipper BA, De La Parra Landa A, Maisel AS. Biomarkers in acute myocardial injury. *Transl Res* 2012;159(4): 252-64
16. Dekker MS, Mosterd A, van 't Hof AW, Hoes AW. Novel biochemical markers in suspected acute coronary syndrome: systematic review and critical appraisal. *Heart* 2010;96(13):1001-1010.
17. Giannitsis E, Kehayova T, Vafaie M, Katus HA. Combined Testing of High-Sensitivity Troponin T and Copeptin on Presentation at Prespecified Cutoffs Improves Rapid Rule-Out of Non-ST-Segment Elevation Myocardial Infarction. *Clin Chem* 2011;57(10):1452-55
18. Schaub N, Reichlin T, Twerenbold R, Reiter M, Steuer S, Bassetti S, et al. Growth Differentiation Factor-15 in the Early

Diagnosis and Risk Stratification of Patients with Acute Chest Pain. *Clin Chem* 2012; 58(2):441-49

19. Eggers KM, Venge P, Lindahl B. High-sensitive cardiac troponin T outperforms novel diagnostic biomarkers in patients with acute chest pain. *Clin Chim Acta* 2012;413(13-14):1135-40
20. Moons KG, Grobbee DE. When should we remain blind and when should our eyes remain open in diagnostic studies? *J Clin Epidemiol* 2002;55(7):633-636.
21. Matveeva EG, Gryczynski Z, Lakowicz JR. Myoglobin immunoassay based on metal particle-enhanced fluorescence. *J Immunol. Methods*. 2005;302(1-2): 26-35.
22. Heeschen C, Dimmeler S, Fichtlscherer S, Hamm CW, Berger J, Simoons ML, et al. Prognostic Value of Placental Growth Factor in Patients With Acute Chest Pain. *JAMA* 2004; 291(4):435-41.
23. Reichlin T, Hochholzer W, Stelzig C, Laule K, Freidank H, Morgenthaler NG, et al. Incremental Value of Copeptin for Rapid Rule Out of Acute Myocardial Infarction*. J Am Coll Cardiol* 2009;54:60–8.
24. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143(1):29-36.
25. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;15(4):361-387.
26. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol.* 2006;59(10):1087-91.
27. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med. 2003*;138(1):W1-12.
28. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ.* 2003;326(7379):41-4.
29. Möckel M, Searle J, Hamm C, Slagman A, Blankenberg S, Huber K, et al. Early discharge using single cardiac troponin and copeptin testing in patients with suspected acute coronary syndrome (ACS): a randomized, controlled clinical process study. Eur Heart J. 2015 Feb 7;36(6):369-76.
30. Kurz K, Giannitsis E, Becker M, Hess G, Zdunek D, Katus HA. Comparison of the new high sensitive cardiac troponin T with myoglobin, h-FABP and cTnT for early identification of myocardial necrosis in the acute coronary syndrome. *Clin Res Cardiol* 2011;100(3):209-15
31. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012;33(18):2252-57
32. Wu AH. Early detection of acute coronary syndromes and risk stratification by multimarker analysis. *Biomark Med* 2007;1(1):45-57
33. Güder G, Brenner S, Angermann CE, Ertl G, Held M, Sachs AP, et al. GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res* 2012;13(1):13
34. Bertens LC, Broekhuizen BD, Naaktgeboren CA, Rutten FH, Hoes AW, van Mourik Y, et al. Use of expert panels to define the reference standard in diagnostic research: a systematic review of published methods and reporting. *PLoS Med.* 2013;10(10):e1001531.
35. Ottenbacher KJ, Ottenbacher HR, Tooth L, Ostir GV. A review of two journals found that articles using multivariable logistic regression frequently did not report commonly recommended assumptions. *J Clin Epidemiol* 2004;57:1147e52.
36. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG.. Prognosis and prognostic research: what, why, and how? *BMJ* 2009;338:b375.

Appendix 1. Specification of biomarker assays

Hs-cTnT was measured with the Elecsys troponin T hs assay fourth generation (Roche Diagnostics) with a lower detecting limit of 3pg/mL. The 99th-percentage cut-off point was ≥14pg/mL. The coefficient of variation (CV) was <10% at 13 pg/mL. PlGF was measured with the Elecsys PlGF assay (Roche Diagnostics) with a measuring range 3-1000pg/mL. The CV was <5% for measured values. sFlt-1 was measured with the Elecsys sFlt-1 assay (Roche Diagnostics) with a measuring range of 10-85000pg/ml. The CV was <5% for measured values. Myoglobin was measured with the Elecsys myoglobin assay (Roche Diagnostics) with a measuring range 21-3000ng/mL. The CV was <10% for all levels. NT-proBNP was measured with the Elecsys proBNP II assay (Roche Diagnostics, Switzerland). The lower detection limit was 5pg/mL and the CV was <5% for measured values. GDF-15 was measured with the GDF15 sandwich immunoradiometric sandwich assay. The lower detection limit was 20ng/L. The intra assay imprecision ranged from 2.85 to 10.6% and the inter assay imprecision ranged from 4.05 to 12.2%. Copeptin was measured with the commercial sandwich immunoluminometric assay (B.R.A.H.M.S. LUMItest CT-proAVP, B.R.A.H.M.S AG, Hennigsdorf/Berlin, Germany). The lower detection limit was 0.4pmol/l, and the functional assay sensitivity (<20% interassay CV) was <1pmol/l. If the measured copeptin level was 'low' we used 1pmol/L.



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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7

ABSTRACT

Background: 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. Currently, 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 sub analysis was performed of a multicenter prospective validation study of the HEART score, consisting of 248 patients who underwent exercise testing within 7 days after presentation in the ED. Outcome is the predictive value of exercise testing in terms of major adverse cardiac events (MACE) within 6 weeks after presentation.

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

Conclusion: In a chest pain population risk-stratified with HEART, exercise testing has only a modest contribution to clinical decision-making. 50% of all tests are non-conclusive, with high rates of false positive tests 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[1-3]. In most guidelines and chest pain protocols, the focus is to identify those patients suspected of an acute coronary syndrome (ACS)[4-5]. 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[6,7]. 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.

The TIMI and GRACE scores were developed for risk assessment in ACS patients[1,8]. These score are applied as well in the much broader category of chest pain patients at the ED. In order to improve diagnostic and therapeutic pathways, we designed the HEART score specifically for all chest pain patients in the ED[9]. The HEART score was validated in three multicenter studies[10-12]. The first was retrospective and yielded promising results[10]. This was followed by the prospective study in 2388 patients at 10 sites from which this is a sub study[11]. The third was an external validation study that was conducted in 2906 patients in the Asia-Pacific region[12]. 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[13]. 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"[14]. 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. Therefore, what is the added value of 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. See Figure 1 for patient flow. 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. Of the original validation study, 7 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.

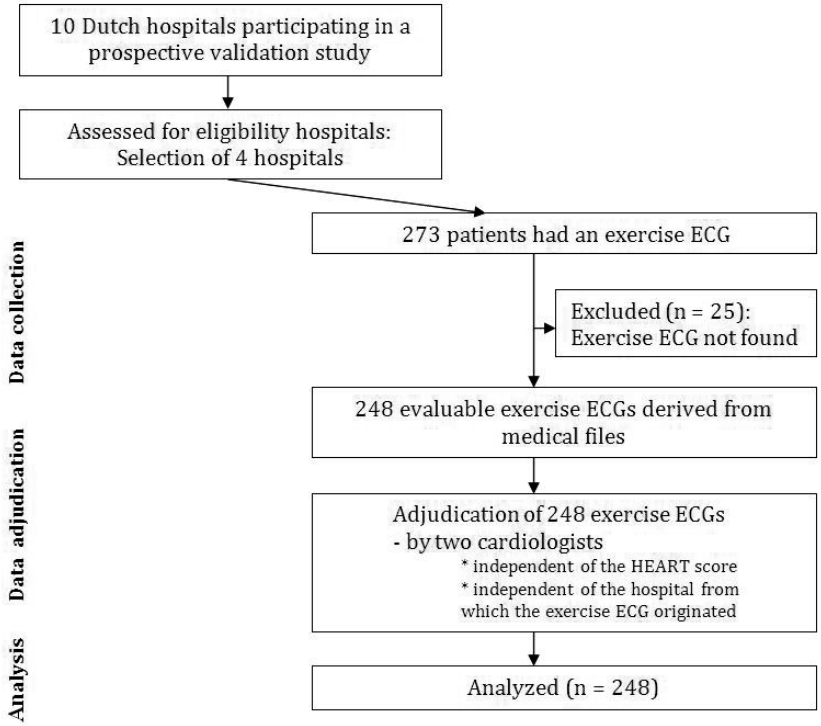
The HEART score

The HEART score contains five components (Table 1). Each component is divided in three categories with 2, 1 or 0 points. For specific explanation of each HEART element, please see previous publications[9,10]. The HEART score was calculated on the basis of computer-entered patient data, without subjective interpretations.

Table 1. The HEART score for chest pain patients

History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Significant ST-depression	2
	Nonspecific 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. Patient flow chart: exercise ECG derivation



Adjudication process

All exercise ECGs were performed with clinical indication, not for research purposes. Since documentation on conclusion of these exercise tests was not always available, we decided to re-read all retrieved exercise ECGs. 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

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. The classification of the exercise ECGs followed the paragraph 'Interpretation of the Exercise Test' of the ACC/AHA practice guidelines[14]. 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 depression ≥1 mm or elevation for at least 60 to 80 milliseconds (ms) after the end of the QRS complex was classified 'significant ST deviation'. 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.

Follow-up and outcome

The outcome measure was the occurrence of MACE within 6 weeks of initial presentation. MACE consists of: AMI, PCI, CABG, significant stenosis with conservative treatment and death due to any cause. Follow up data concerning MACE 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.

Data analysis

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). Statistical evaluations were performed according to Cook[16].

RESULTS

Study population

The 4 participating hospitals of this sub study included 767 patients, of which 273 had an exercise test (35.6%). Of these 273 patients, 248 (90.8%) had an evaluable exercise test, performed before any coronary catheter investigation and not in the setting of myocardial stress imaging. The contribution of the four hospitals was: Universitair Medisch Centrum Utrecht 26%, Gelre Apeldoorn 27%, Medisch Centrum Haaglanden Westeinde 34%, Medisch Centrum Haaglanden Antoniushove 44%. 82 (33.1%) exercise tests were performed on the day of presentation and the other 166 (66.9%) within 1 week after presentation. Patient characteristics are given in Table 2a.

Endpoints

A MACE within 6 weeks occurred in 25 (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. 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 2a. Baseline characteristics

Patient characteristics, N (% or SD)	Patients with an ET	All patients sub study
Study group	248 (32.9)	754 (100)
Age*	59.4 (13.1)	59.3 (16.3)
Male gender	153 (61.7)	420 (55.7)
Systolic blood pressure*	146.6 (24.0)	145.2 (26.2)
Diastolic blood pressure*	78.8 (14.9)	78.0 (15.1)
Diabetes Mellitus	53 (21.4)	161 (21.4)
Smoker	86 (34.7)	265 (35.1)
Hypercholesterolemia	104 (41.9)	272 (36.1)
Hypertension	105 (42.3)	305 (40.5)
Family History	98 (39.1)	251 (33.3)
Obesity	56 (22.6)	178 (23.6)
History of AMI	37 (14.9)	94 (12.5)
History of CABG	36 (14.5)	82 (10.9)
History of PCI	61 (24.6)	142 (18.9)
History of Stroke	11 (4.4)	39 (5.2)
History of peripheral arterial disease	12 (4.7)	44 (5.8)
HEART score*	4.3 (1.8)	4.1 (2.1)
MACE within six weeks	25 (10.1)	100 (13.3)
AMI	9 (3.6)	39 (5.2)
PCI	14 (5.6)	57 (7.6)
CABG	3 (1.2)	21 (2.8)
Significant stenosis	4(1.6)	11 (1.5)
Death	0	6 (0.8)

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

ECG during exercise

We recorded information on the 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 and classification of the technical quality of the test. The results are shown in Table 2b. 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 1 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.

Table 2b. Exercise ECG characteristics

Exercise ECG characteristics, N (% or SD)	Patients with an ET
Use of Beta-blockers during exercise ECG	100 (40.3)
Exercise ECG performed on the day of presentation	82 (33.1)
Pre-test ECG entirely normal	158 (63.7)
Maximum heart frequency in bpm*	137.1 (26.7)
Maximum exercise performance in Watts (228 patients)*	133.2 (56.6)
Maximum exercise performance in METS (19 patients)*	11.4 (3.3)
Duration of the exercise tests in minutes*	6:11 (2:21)
Maximal systolic blood pressure in mmHg*	192.0 (31.9)
Maximal diastolic blood pressure in mmHg*	90.6 (24.3)
Occurrence of symptoms during exercise	212 (85.5)

*Mean (SD)
ET: exercise test, METS: metabolic equivalents of task

Adjudication of exercise tests

A (borderline) negative test occurred in 99 (39.9%) of the patients. Almost half of the patients (49.2%) had a non-conclusive exercise ECG. A (borderline) positive test occurred in 27 (10.9%) of the patients. The exercise ECG results for the different risk-groups, stratified with HEART in relation to the occurrence of MACE are given in Table 3. For low-risk patients, of the positive adjudicated exercise tests, 100% (7/7) are false positives, 2% (1/53) are false negatives and 29% (24/84) exercise tests are non-conclusive. For the intermediate-group (HEART 4-6), forty-two of in total 136 exercise tests correctly predict that there is a no risk of MACE in this subgroup; once again a high percentage of non-conclusive tests (60%). When an exercise test in this group is adjudicated as positive, there is as much chance it will be true positive as false positive. The exercise ECG results for the high-risk-group (HEART≥7) in relation to the occurrence of MACE are also given in Table 3. Table 4 shows sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of exercise ECG in the different subgroups of HEART.

Table 3. Outcome exercise ECG in relation to occurrence of MACE in different risk groups, stratified with the HEART score

			Occurrence of MACE		
			MACE	No MACE	**Total**
Low-risk HEART patients					
Exercise ECG	Positive		0 (0%)	7 (9%)	**7 (8%)**
	Non-conclusive		1 (50%)	23 (28%)	**24 (29%)**
	Negative		1 (50%)	52 (63%)	**53 (63%)**
		Total	**2 (100%)**	**82 (100%)**	**84 (100%)**
Intermediate-risk HEART patients					
Exercise ECG	Positive		6 (40%)	6 (50%)	**12 (9%)**
	Non-conclusive		9 (60%)	73 (45%)	**82 (60%)**
	Negative		0 (0%)	42 (5%)	**42 (31%)**
		Total	**15 (100%)**	**121 (100%)**	**136 (100%)**
High-risk HEART patients					
Exercise ECG	Positive		4 (50%)	4 (20%)	**8 (29%)**
	Non-conclusive		3 (38%)	13 (65%)	**16 (57%)**
	Negative		1 (12%)	3 (15%)	**4 (14%)**
		Total	**8 (100%)**	**20 (100%)**	**28 (100%)**

Table 4. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the different HEART risk groups, given with 95% CI (non-conclusive tests were not included in this calculation)

		Exercise ECG			
		Sensitivity	**Specificity**	**PPV**	**NPV**
HEART	Low risk	0	0.88 (0.80-0.95)	0 (0-0.44)	0.981 (0.89-1.00)
	Intermediate risk	1.0	0.88 (0.77-0.95)	0.5 (0.22-0.78)	0.736 (0.60-0.84)
	High risk	0.80 (0.38-0.99)	0.43 (0.12-0.77)	0.5 (0.17-0.83)	0.75 (0.22-0.99)

DISCUSSION

Exercise testing after HEART score assessment only 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. This underlines the results of Gaibazzi et al (2011) in a somewhat smaller population of only 53 patients with an exercise ECG out of which 18 were false negative and 6 false positive tests[17]. These authors concluded that "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"[17]. Furthermore, 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[18]. 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%[19]. Blankstein et al. demonstrated that a positive exercise treadmill testing had a limited sensitivity but high specificity for the detection of >50% stenosis by CT angiography[20]. Lastly, the American Heart Association formulated a statement regarding testing of low-risk chest pain patients[21]. In this, exercise treadmill is part of the recommendations. Numerous studies support the use of exercise treadmill stress. Nevertheless, they also mention the low positive predictive value of exercise testing.

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. 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.

Limitations

The exercise test in cardiology was not designed to predict adverse outcomes in acute chest pain patients, but to diagnose coronary ischemia in patients with stable angina. 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"[14].

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. Lastly, given the low event rate, with for example the low sensitivity (0%) but high specificity in the low-risk group could be wrongly estimated. If there was even one truly positive test, the sensitivity jumps to 50%.

CONCLUSION

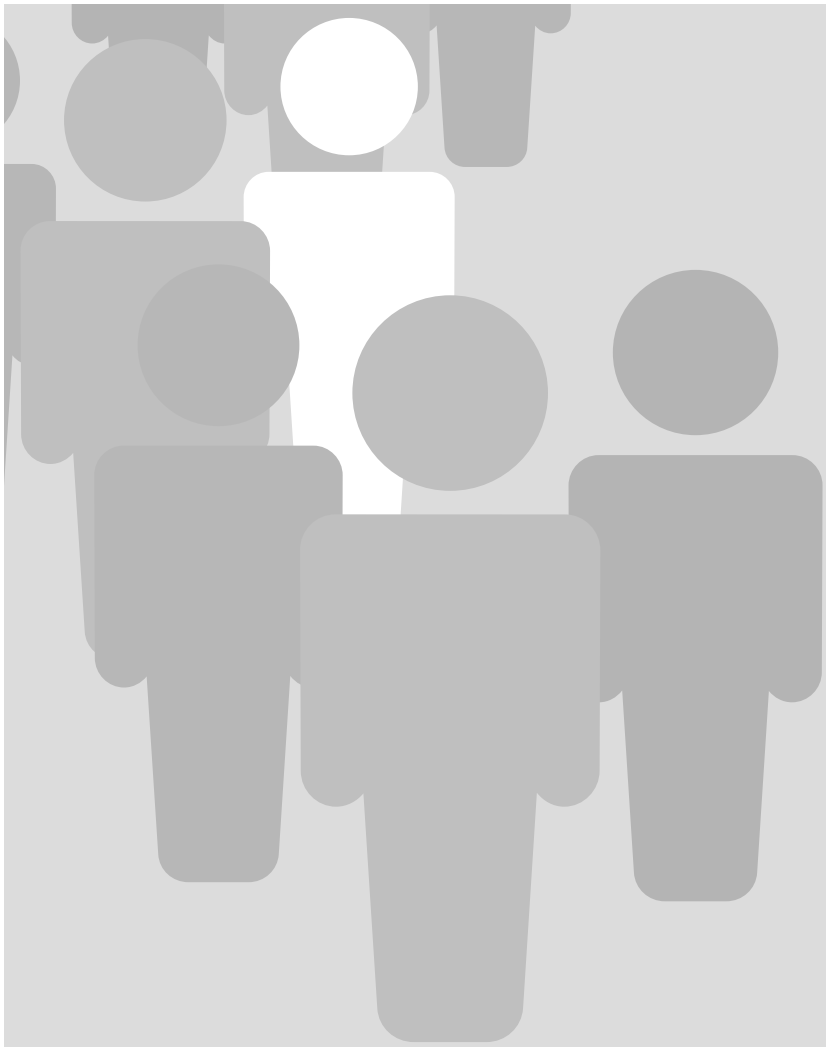
In a chest pain population, risk-stratified with the HEART score, the exercise ECG has only a modest contribution to clinical decision-making. Notably, in about half the patients in all risk groups the test is non-conclusive, and the rate of false positive tests is high in all three risk-groups. Only 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. Furthermore, one recommendation could be that physicians should try to perform conclusive exercise tests.

REFERENCES

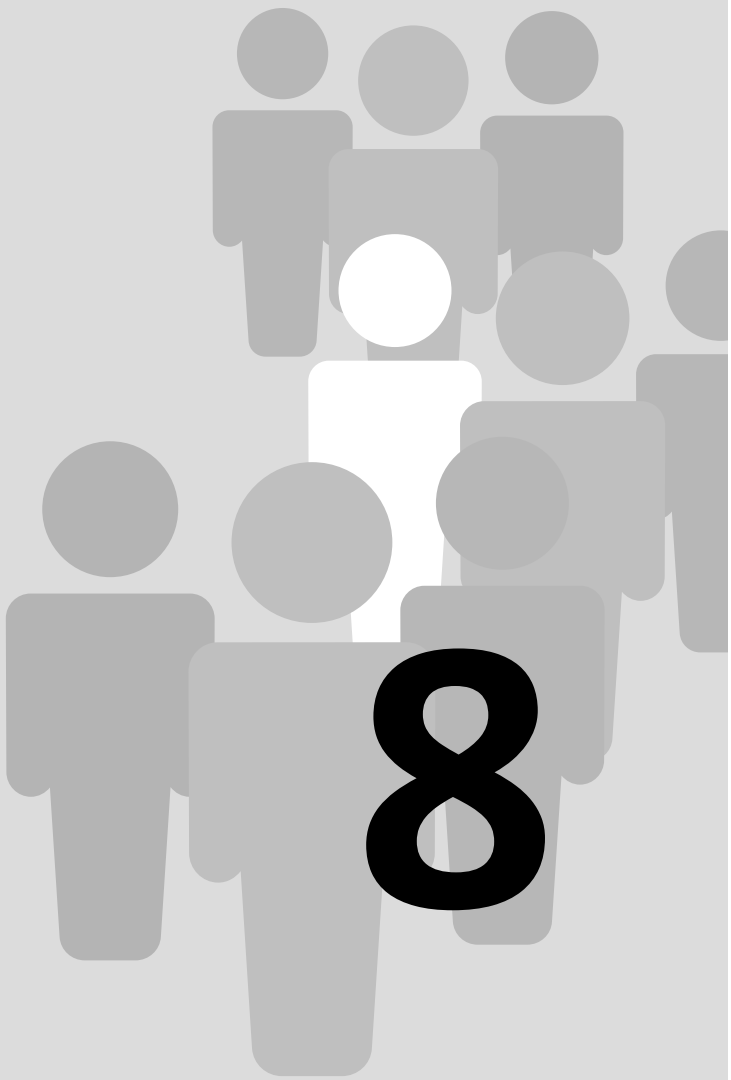
1. Ramsay G, Podogrodzka M, McClure C, Fox KAA. Risk prediction in patients presenting with suspected cardiac pain: The GRACE and TMI risk scores versus clinical evaluation. QJM 2007;100:11-18.
2. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart 2005;91:229-230.
3. Kirchberger I, Heier M, Wende R, von Scheidt W, Meisinger C. The patient's interpretation of myocardial infarction symptoms and its role in the decision process to seek treatment: the MONICA/KORA Myocardial Infarction Registry. Clin Res Cardiol. 2012 May 23.
4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/Non ST-elevation myocardial infarction. JACC 2007;50:e1-e157.
5. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Avilés FF, et al. ESC guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1598-1660.
6. Post F, Giannitsis E, Riemer T, Maier LS, Schmitt C, Schumacher B, et al. Pre- and early in-hospital procedures in patients with acute coronary syndromes: first results of the "German chest pain unit registry". Clin Res Cardiol. 2012 Jul 25.
7. Keller T, Post F, Tzikas S, Schneider A, Arnolds S, Scheiba O, et al. Improved outcome in acute coronary syndrome by establishing a chest pain unit. Clin Res Cardiol. 2010 Mar;99(3):149-55.
8. Stracke S, Dörr O, Heidt MC, Gündüz D, Neuhof C, Parahuleva M, et al. GRACE risk score as predictor of in-hospital mortality in patients with chest pain. Clin Res Cardiol. 2010 Oct;99(10):627-31.
9. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J 2008;16:191-6.
10. Backus BE, Six AJ, Kelder JC, Mast TP, Akker F van den, Mast G, et al. Chest pain in the emergency room. A multicenter validation of the HEART score. Crit Pathways in Cardiology 2010;9:164-169.
11. Backus BE, Six AJ, Kelder JC, Bosschaert MAR, Mast EG, Mosterd A, et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol 2013:S0167–5273.
12. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, et al. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. Crit Path Car 2013;12: 121–126.
13. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl J Med. 1979;300:1350-1358.
14. Gibbons RJ, Antman EM, Alpert JS Faxon DP, Fuster V, Gregatores G, et al. ACC/AHA Guideline update for exercise testing. JACC 2002;40:1531-40.
15. R Development Core Team (2009). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0.
16. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. Clin Chem 2008;54(1):17-23.
17. Gaibazzi N, Reverberi C, Badano L. Usefulness of Contrast Stress-Echocardiography or Exercise-Electrocardiography to Predict Long-Term Acute Coronary Syndromes in Patients Presenting With Chest Pain Without Electrocardiographic Abnormalities or 12-Hour Troponin Elevation. Am J Cardiol 2011;107:161–167.
18. Mahler SA, Hiestand BC, Goff DC, Hoekstra JW, Miller CD. Can the HEART score safely reduce stress testing and cardiac imaging in patients at low risk for major adverse cardiac events? Crit Pathways in Cardiol 2011;10:128-133.
19. Gibler WB, Runyon JP, Levy RC, Sayre MR, Kacich R, Hattemer CR, et al. A rapid diagnostic and treatment center for patients with chest pain in the emergency department. Ann Emerg Med 1995;25:1-8.
20. Blankstein R, Ahmed W, Bamberg F, Rogers IS, Schlett CL, Nasir K, et al. Comparison of Exercise Treadmill Testing With Cardiac CT

Angiography Among Patients Presenting To The Emergency Room With Chest Pain: ROMICAT Study. Circ Cardiovasc Imaging 2012;5;233-242.

21. Amsterdam EA, Kirk JD, Bluemke DA, Diercks D, Farkouh ME, Garvey JL, et al. Testing of low-risk patients presenting to the emergency department with chest pain: a scientific statement from the American Heart Association. Circulation. 2010;122(17):1756-76.



Discussion



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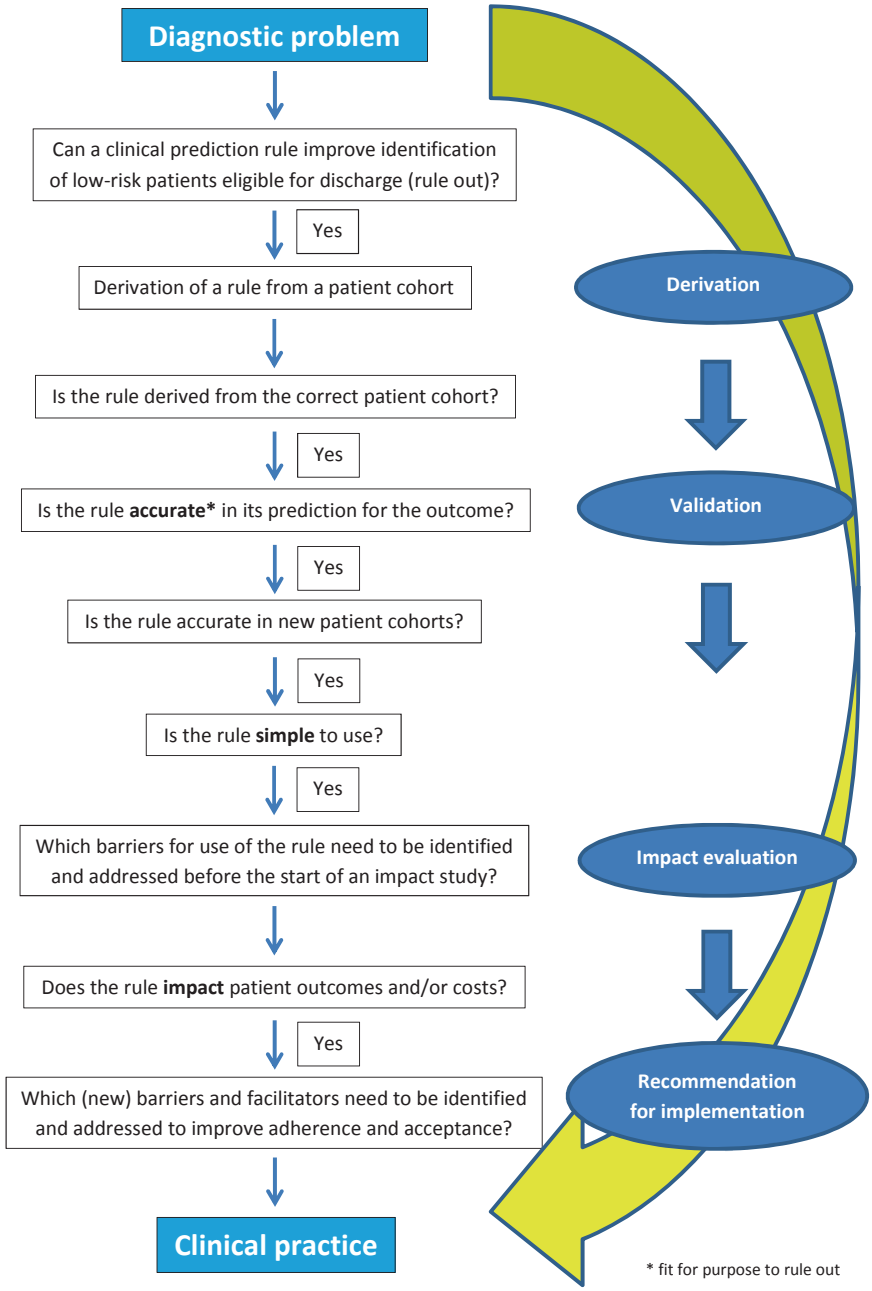
"So we have a promising clinical prediction rule: what's next?"

Chest pain and clinical prediction rules

Ruling out acute coronary syndrome (ACS) in patients presenting with chest pain remains a major diagnostic dilemma. Early identification of ACS is crucial to start prompt treatment and improve the prognosis of these patients[1]. Various clinical prediction rules have been developed to assist physicians in the early identification of ACS[2-9], and their use is recommended in all international guidelines on (suspected) ACS, as these rules appear superior to clinical assessment alone[10]. Examples of rules are the TIMI and GRACE scores, but over the past 10 years several other rules, such as the HEART score, have been developed2[-9]. Clinical prediction rules consist of multiple pieces of information ("predictors") from history, physical examination and frequently also basic laboratory tests[11]. These predictors are combined into a total score which predicts the probability of a specific outcome for an individual patient. A useful clinical prediction rule should not only present the clinician with an absolute probability or risk category, but also with a recommendation for subsequent patient management, such as further testing or the initiation of specific treatments (typically when the probability of the disease is high) or refraining from further testing and for example early discharge from the emergency department, when the probability of disease is low[12].

In order to be endorsed and routinely used in clinical practice, a clinical prediction rule has to meet several criteria (Figure 1). Importantly, (1) the rule has to be accurate in its prediction for the condition or disease of interest, (2) be simple in its use (preferably at the bedside) and (3) improve patients' outcomes or reduce health care costs. Several available clinical prediction rules for chest pain patients meet the first (and to a lesser extent) the second criterion. Although for many rules it is not investigated, and thus unknown, what the impact of their application in daily practice is (the third criterion), some are even recommended in international guidelines. The fact that many recommended clinical prediction rules are not calculated, or calculated without active adherence to the rules' recommendation for patient management[13], may (at least partly) be attributable to the lack of these impact studies. In this general discussion we take a closer look at the different ways to evaluate impact of a clinical prediction rule and to ensure its application in clinical practice. In particular, the role and value of impact studies are examined.

Figure 1. Evaluation journey of a clinical prediction rule: from clinical problem to application in clinical practice



Evaluation journey of a clinical prediction rule

The evaluation journey of a clinical prediction rule typically has several phases, as depicted in Figure 1[14]. First, the rule is developed, ideally in a cohort of patients reflecting the population in whom the rule will be used in practice. By measuring the potential relevant predictors that will be available in practice and the outcome of interest, a clinical prediction rule can be derived through statistical modelling, such as logistic regression or a Cox' proportional hazard model. An interesting alternative to developing a prediction rule based in mathematical modelling is to derive a prediction rule based on clinical experience alone. This has the important advantage that one can choose a simple score, based on a few clinical items that are considered important by other clinicians as well as easy to assess, greatly increasing the applicability of the rule. An obvious disadvantage of such a pragmatic way of developing a prediction rule is the poorer performance of such a rule in predicting the outcome, because its derivation is not based on real data. A famous example of a rule developed in this way is the Apgar score. The score predicts mortality in neonates, based on 5 items (each scored 0, 1 or 2 points) and was developed by Virginia Apgar in the 1950s[15]. The Agpar score was only validated for its predictive performance (which was actually good) many years after its development; at the time the score was already applied worldwide. The latter indicates that rules based on a few simple clinical items are more likely to be applied in daily practice. Also the HEART score (in contrast to the TIMI and GRACE scores) was developed based on clinical experience, including 5 items and total score ranging from 0 to 10.

A critical next step in the evaluation of a derived prediction rule is to examine whether the performance in new patients is comparable to the performance in the original cohort; this is known as external validation[16]. Such a validation is even more crucial when the score is not derived from data but based on clinical experience, as is the HEART score. The performance of prediction rules often significantly deteriorates in new patients compared to the performance in the original development cohort[17-20]. In this phase of the evaluation it becomes clear which prediction rule really has potential, and which rule does not meet certain minimal criteria necessary to fulfil its intended role in clinical practice. These external validation studies also offer the opportunity to zoom in on the intended use of the clinical prediction rule in practice.

In case of risk stratification of patients with chest pain, the identification of patients at low risk could lead to early discharge or further management outside the hospital. Such a role of a prediction rule is referred to as triage. To serve as a triage instrument, the rules' use should be safe meaning that the frequency of the outcome in the low-risk group should not exceed a specific, clinically acceptable level. Furthermore, the number of patients identified as low risk should be sufficiently large to generate improvements in patient management,

for example in terms of fewer additional diagnostic tests or hospital admissions (and thus a reduction in costs) or in patients' quality of life. Some information on these items can be obtained in external validation studies, such as the proportion of patients that can be classified as low risk by the prediction rule and the frequency of false-negatives or –positives in these patients. However, these validation studies do not provide direct evidence whether routine use of the rule will lead to benefits for patients or health care.

Measuring impact

It is tempting to assume that if external validation studies show promising results, the clinical prediction rule is ready to be introduced in clinical practice. Indeed, the evaluation journey of many prediction rules stop after external validation, without further investigation of the impact of implementation of such a rule[14,21]. Increasingly, the need for impact evaluation is highlighted or even demanded to explicitly demonstrate that the routine use of a clinical prediction rule contributes to patient outcomes, guides patient management and leads to potential savings. Such direct evidence can be generated with an impact study or cost-effectiveness study.

We performed such an impact trial for the HEART score (Figure 2), a clinical prediction rule for chest pain patients at the emergency department. It was developed in 2007 and had promising results in external validation studies (Table 1). Our main findings of this HEART-Impact trial were that routine use of the HEART score is just as safe as usual care (i.e. without the HEART score) for initial assessment of chest pain patients at the emergency department. The increase in proportion of early discharge and decrease in use of health care resources following the initial assessment was however limited and lower than anticipated.

In the following sections, we will discuss the following three key issues when considering an impact study: (1) whether and when to perform an impact study, (2) optimal study design of an impact study and (3) possible barriers when enrolling the intervention in an impact study. We will use our own experiences with the HEART-Impact trial to illustrate these key issues.

(1) Whether and when to evaluate the impact of a clinical prediction rule?

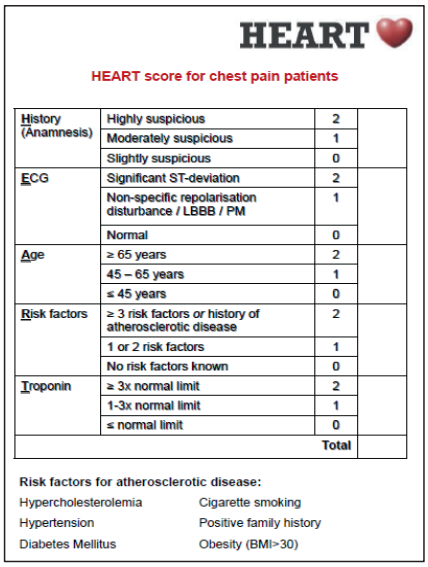
Impact studies are conducted to assess the real-life effect of an intervention (or in our case a clinical prediction rule). However, performing an impact study takes time, effort and comes with high costs. These operational and financial efforts should be weighed against the potential improvement of patient outcomes, optimization of patient management and possible future savings. Therefore, only clinical prediction rules with promising results during validation should be taken to this next level of evaluation: measuring impact in daily clinical practice[22].

Table 1. Characteristics of derivation and validation studies of the HEART score

	DERIVATION	VALIDATION I	VALIDATION II	VALIDATION III	VALIDATION IV
Date	2006	2006	2007-2010	2008-2009	2008-2010
Authors	Six et al.	Backus et al.	Six et al.	Backus et al.	Mahler et al.
Location	1 hospital, The Netherlands	4 hospitals, The Netherlands	14 hospitals, 9 countries in Australasia	10 hospitals, The Netherlands	1 hospital, USA
Nr of patients	122	2,161	2,906	2,388	1,070
Design	Retrospective	Retrospective	Retrospective analysis of prospective data	Prospective	Registry
Inclusion criteria (domain)	Any chest pain patient admitted to ED	Any chest pain patient admitted to ED	Possible cardiac symptoms included acute chest, epigastric, neck, jaw, or arm pain; or discomfort or pressure without an apparent noncardiac source.	Any chest pain patient admitted to ED	Chest pain patients, but TIMI risk score <2 + clinical assessment "low risk"; Normal or non-diagnostic ECG; Negative first set of troponin I
Exclusion criteria	STEMI	STEMI	Clear cause other than an ACS; STEMI; Incomplete data for HEART score	STEMI	Not mentioned
Primary endpoints	AMI, PCI, CABG, death	MACE: AMI, PCI, CABG, death	MACE: AMI, emergency PCI, CABG, death (unless clearly non-cardiac).	MACE: AMI, PCI, CABG, death	MACE: AMI, PCI, CABG, all-cause mortality
Follow-up	6 weeks	6 weeks	30 days	6 weeks	30 days
Incidence of MACE	24.1% (all outcomes)	18.0% (MACE)	12.9% (MACE)	17.0% (MACE)	1.1% (MACE)
Incidence of MACE components	13.3% AMI, 11.6% PCI, 5.0% CABG, 1.6% death	AMI 10.5%, 9.3% PCI, 4.1% CABG, 1.5% death	STEMI; 19 patients, NSTEMI; 353 patients. 19 patients (0.7%) underwent emergency PCI or CABG, 9 patients (0.3%) died	6.4% AMI, 10.5% PCI, 2.8% CABG, 1.8% stenosis managed conservatively, 0.7% death	Not mentioned
	DERIVATION	**VALIDATION I**	**VALIDATION II**	**VALIDATION III**	**VALIDATION IV**
Risk categories with % of outcome	Low risk (0-3): 2.5% Intermed-risk (4-6): 20.3% High risk (7-10): 72.7%	Low risk: 1.0% Intermed-risk: 11.6% High risk: 65.2%	Low-risk: 1.7% High-risk: 43%.	Low-risk: 1.7% Intermed-risk: 16.6% High-risk: 50.1%	Low-risk: 0.6% → reduced cardiac testing by 85%;
Accuracy	Not mentioned	C-statistic: 0.90	C-statistic 0.83 (0.81–0.85)	C-statistic 0.83	Combination of serial troponin or HEART score 3 sensitivity of 100% (95% CI: 72–100%) → reduced cardiac testing by 82%

STEMI: ST-elevation myocardial infarction, AMI: acute myocardial infarction, ACS: acute coronary syndrome, PCI: percutaneous coronary intervention, CABG:coronary arterial bypass grafting

Figure 2. The HEART score for chest pain patients



HEART

HEART score for chest pain patients

History (Anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-deviation	2	
	Non-specific repolarisation disturbance / LBBB / PM	1	
	Normal	0	
Age	≥ 65 years	2	
	45 – 65 years	1	
	≤ 45 years	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 for atherosclerotic disease:

Hypercholesterolemia	Cigarette smoking
Hypertension	Positive family history
Diabetes Mellitus	Obesity (BMI>30)

Proposed policy

HEART score	Percentage of patients	Percentage of MACE	Proposed policy
0-3	32%	1.6%	Early discharge from ED
4-6	51%	13%	Observation & non-invasive testing or imaging
7-10	17%	50%	Early invasive treatment (CAG)

In particular, external validation studies can zoom in on specific issues that are relevant for the intended role in clinical practice such as how many patients can be classified as low risk by the prediction rule and what the frequency of "events" (e.g. the diagnosis in diagnostic prediction rules or the complication (e.g. mortality) in prognostic rules) is in these low-risk patients. These results may already indicate that a rule is not fit for purpose, e.g. when the number of false-negatives, in our example the proportion of patients with ACS in the low-risk group, is too high to be clinically acceptable. It is advantageous to fully exploit the value of external validation studies as these studies are relatively easy to perform: all patients can be included, undergo the prediction rule and their outcomes can be assessed without much interference of daily practice. With increasing certainty that the expected advantages of the use of a prediction rule will indeed happen in clinical practice, the necessity to perform an impact study may not be felt anymore[23]. However, without execution of the full consequence of the rule (e.g. early discharge without further testing in patients with a low HEART score), the safety of such a directive use of the rule can never be quantified completely.

Despite extensive validation studies with promising results there may be a demand for performing an impact study. The rationale for an impact study is that the combined effects of applying the rule and the subsequent patient management may be difficult to predict from the results of validation studies. This may be attributable to several phenomena. For example, the prediction rule is not calculated in daily practice because of time constraints, or too complicated to calculate. Importantly, even when the rule is routine calculated in

individual patients, the recommended policy, such as hospital admission or no further testing, may not be adhered to, perhaps because of fear for false-negative scores. The latter may be especially important in suspected ACS, where patient management is often "defensive" because of the potential severe consequences of false-negatives. Validation studies, where typically the score is calculated retrospectively or prospectively, but patient management is not based the individual scores, can, thus, never fully mimic the real-life application of prediction rules. This is illustrated by our studies.

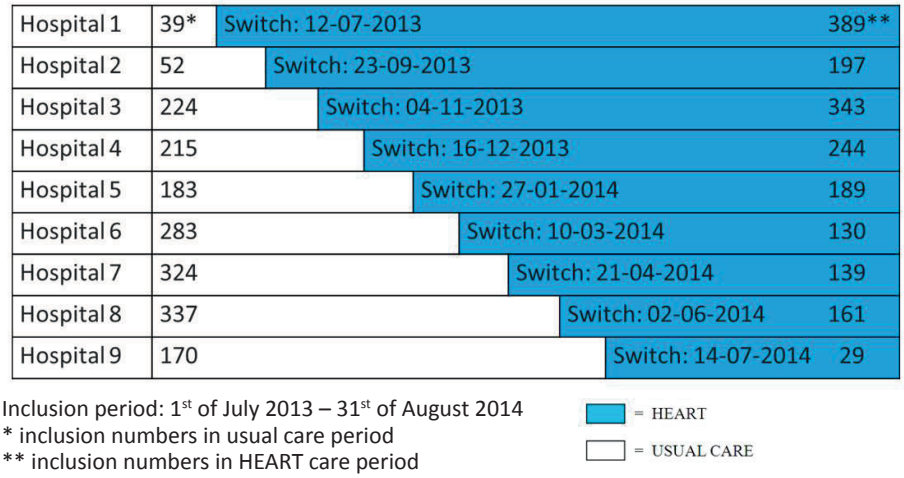
Although the validation studies of the HEART score yielded very promising results, clinicians remained uncertain about safety. Apparently they wondered whether patients with a low HEART score who could be discharged early from the emergency department, might still develop adverse cardiac events at home. Indeed, in our case there are two reasons that necessitate the evaluation of the impact of the HEART score in clinical practice. First, is the routine use of the HEART score safe when in patients with low scores it is recommended to go for early discharge from the emergency department without further testing or observation? Second, if applied in practice, will it result in a decrease of the use of health care resources, will a decrease of health care use at the emergency department and hospital result in transfer of care to the general practitioner, or will more patients return to the emergency department, because they feel they were not assessed properly? The benefit of an impact study is that you can (and must) measure all possible positive *and* negative effects of using the clinical prediction rule both on patients and on health care in general.

(2) Study design: how should we evaluate the impact of a clinical prediction rule?
When the decision is made to perform an impact study, there are a number of design issues to take into account. We focus on (a) the choice of study design and (b) how to define and control the intervention.

(a) Study design. Randomized controlled trials are considered the ultimate yardstick for measuring the impact of a new intervention by making a head-to-head comparison between existing care ("usual care") versus the new care guided by the prediction rule in comparable patient groups generated by randomization. One variation of a randomized controlled trial that has recently being advocated to evaluate impact is the stepped wedge cluster randomized design[24]. In a stepped wedge design, health care units (the clusters; e.g. hospitals, primary care practices) are randomized in the timing when to switch from usual care to the intervention (Figure 3). Stepped wedge designs are increasingly used to evaluate the real-life effectiveness of interventions because of the following features: (i) cluster type of design: the implementation of a prediction rule often requires a cluster type of design to prevent contamination. Training and instruction is often needed which is best done in clusters; (ii) each hospital switches to the intervention, which may

enhance participation of clusters; (iii) there is a one directional change from usual care to intervention care, reducing the risk of contamination. All hospitals end with the new intervention, so they can continue in case of positive findings. One other main advantage of this design is that you can measure the effect of the intervention within each cluster (within-hospital comparison), offering the opportunity to examine whether the effect is constant between clusters, and in case of heterogeneous results explore possible reasons.

Figure 3. Stepped wedge design in the participating hospitals of the HEART-Impact trial



Inclusion period: 1st of July 2013 – 31st of August 2014
* inclusion numbers in usual care period
** inclusion numbers in HEART care period

However, the stepped wedge design has also certain disadvantages. Especially, the fact that the design requires all hospitals to start simultaneously, is an important logistical challenge. Furthermore, once the trial has started and the first switch in the first hospital has taken place, the timing of switches in care become fixed (e.g. every six weeks a hospital needs to switch from usual care to intervention care). It reduces the flexibility to extend your study period (e.g. to increase the inclusion period or the follow-up time) after the first switch, in case of disappointing inclusion rates or logistical issues. Alternative designs, such as before-after studies or external comparison studies (comparing several hospitals), may not have these disadvantages, but lack the considerable advantages of (stepped wedge) cluster randomized trials. Apart from stepped wedge cluster randomized trials, also parallel randomized trials applying randomization of individual patients or clusters are possible, but the main disadvantage of individual randomization is contamination and of cluster randomization is the incomparability of patients within clusters.

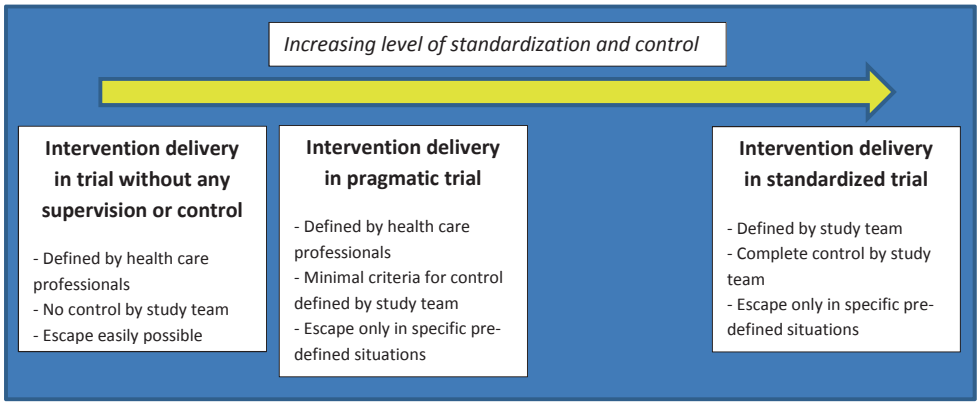
(b) How to define and control the intervention. It may be a challenge to define and control the delivery of interventions in a pragmatic impact trial. Notably, in the case of a clinical prediction rule, the intervention is the combination of applying the rule itself with the recommendations for patient management resulting from the rule. Two extremes in approaches for implementation during an impact trial are: a very strictly defined protocol and no flexibility how the intervention should be delivered; or just a general description of what the intervention should be without details and further monitoring by the researcher (Figure 4). In our HEART-Impact trial, we felt it to be a true dilemma to stay pragmatic, when cardiologists did not adhere to the HEART protocol, although we wanted to assess how the HEART score protocol really impacts the process of care when closely adhered to. A pragmatic approach is described as an intervention that is supplied by the study team, but further enrolled by the physicians themselves, without further control by the study team. The way the physicians use (or do not use) your intervention is defined by the health care professionals themselves. It may lead to variation how the intervention is applied between clusters, and physicians may overrule the protocol too easily. Certainly in case of a prediction rule, which is a decision support tool, physicians should have this option, but when adherence to the recommendations it very low, the potential impact of the prediction rule is underestimated[25]. To examine the optimal potential effect of your intervention, one approach could be to standardize your intervention as much as possible, for example with the installation of a research nurse 24/7 at the emergency department who monitors whether everyone adheres to the protocol ("adhere to the clinical prediction rule, unless…"). The results of such a trial will reflect the maximal effect, which indeed may be different when applied to other (less standardized) settings. However, the results of such a strict trial may convince cardiologists that the HEART score is truly safe to use, increasing future implementation and use of the score and adherence to the patient management recommendations after the impact trial.

The recently developed PRECIS-2 tool can help trialists to make design decisions consistent with the intended purpose of a trial, and decide when a pragmatic approach is the best option[26]. Hawe et al. advise that researchers examining more complex interventions should standardize only the function and process of the intervention, not the components themselves, thus allowing the form to be tailored to local conditions, improving effectiveness[27]. We agree with this statement when evaluating the impact of an intervention, and therefore researchers should not equal "pragmatic" with "doing nothing to ensure adherence to your intervention, without any supervision or control by the study team". Instead they should always standardize certain aspects of their intervention, and formulate minimal criteria to be monitored and furthermore they should give feedback to researchers in case of non-adherence, also in a pragmatic trial.

This is also shown in Figure 4 with the middle box "Intervention delivery in pragmatic trial". Otherwise, such a complete pragmatic approach without any supervision may result in the absence of effect, and it remains unclear whether the rule and corresponding guidance is ineffective or whether there are major barriers in the implementation of this new approach in daily care.

Our own HEART-Impact trial had a pragmatic approach: we educated the physicians before and during the trial how to use the score and how to adhere to the protocol and we repeatedly reminded them of the necessity for adherence throughout the trial. However, we did not execute a strict control of the adherence at the ED. As we mentioned, our measured effects on patient outcomes and savings during the trial were limited. The potential barriers to changing from usual care to the intervention care including prediction rule are discussed in the next section.

Figure 4. Implementation of a complex intervention: trial without any supervision versus a more pragmatic approach versus a completely standardized approach



(3) Possible barriers when enrolling the intervention in an impact trial

Our hypothesis was that with the routine use of a clinical prediction rule (i.e. the HEART score), assessment of patients with chest pain would be improved, notably by promoting earlier discharge of low-risk patients from the emergency department without additional testing (e.g. stress testing or imaging) and by increasing early invasive treatment in high-risk patients. This could result in potential savings, as shown in several small studies[28-30]. However, on beforehand and during the HEART-Impact trial, clinicians mentioned potential barriers for adherence to patient management recommendations following from the HEART score. We will discuss these encountered barriers in more detail below according to the three different contexts described by Grol et al., namely practice environment, prevailing opinion and knowledge and attitudes[31,32].

Practice environment (organisational context)

- Financial disincentives — Hospitals and medical departments receive compensation by insurance companies for certain procedures and actions. Unfortunately, this financial reimbursement system mostly favours action, testing and hospitalization, instead of favouring withholding of treatment, transfer of care back to the general practitioner, or early discharge.
- Organisational constraints — Hospital have contracts with insurance companies, thus needs to adhere to certain policies and regulations. Furthermore, physicians adhere to several national and/or international professional guidelines. When the new policy is in conflict with these contracts or guidelines, implementation may become more difficult to achieve. See also "Prevailing opinion – Standards of practice".
- Perception of liability —Among some clinicians there was a lack of trust in the score's safety, which may possibly be an explanation for the increase of out-patient clinic visits observed during HEART care (although this was not statistically significant after adjustment for clustering and time). Several participating cardiologists were hesitant to actively use the HEART score and discharge low-risk patients early from the emergency department.

Prevailing opinion (social context)

- Standards of practice — The HEART score only includes a single troponin measurement in its calculation. After this single troponin, the HEART score can be calculated and the recommended policy can be followed. It implies that low-risk patients would be discharged directly after this first troponin measurement. However, many clinical guidelines recommend serial troponin measurement after 3 hours after arrival at the emergency department in all patients[10]. The new European guidelines just implemented a serial troponin measurement after 1 hour[10]. This would possibly have been an alternative to this 3-hour serial troponin measurement, since a measurement after 1 hour will still result in a considerable shorter length of stay at the emergency department, compared to a measurement after 3 hours.
- Opinion leaders — We noticed there were several key persons (such as heads of the department) who had some reservations to our proposed protocol, even though the group of cardiologists as a whole agreed to participate.

Knowledge and attitudes (professional context)

- Clinical uncertainty — In case of chest pain, which can be caused by the life-threatening disease of ACS, physicians strive to minimize the number of false-negatives. It is known that it tends to lead to an overestimation by the physician of pre-test probability of ACS in chest pain patients[33]. Literature on chest pain at the emergency department

report false-negative rate of up to 6%[34], as well as an estimated incidence of unexpected sudden cardiac death around 0.1%[35]. One cardiologist mentioned: "there is no particular risk of the HEART score itself, but only a general risk of unexpected sudden cardiac death and missed ACS, which is something we will have to accept". However, accepting this inevitable risk is difficult in daily practice and poses a dilemma for both physician, patient and society[33].

In view of the limited effects we observed on patient care and health care utilization the question arises whether more attention should have been given to these barriers, perhaps even before initiating the trial, for example with qualitative methods such as interviews. Craig et al. mention that "a good theoretical understanding is needed of how the intervention causes change, so that weak links in the causal chains can be identified and strengthened"[36]. They furthermore pose several questions to ask yourself when implementing an intervention, including: "have you done enough piloting and feasibility work to be confident that the intervention can be delivered as intended? Can you make safe assumptions about effect sizes and variability, and rates of recruitment and retention in the main evaluation study?" Peters et al. suggest in their paper on implementation science that since there are "actors" who need to start using the intended intervention, "one important implication is that often these actors should be intimately involved in the identification, design, and conduct phases of research and not just be targets for dissemination of study results"[37].

Even after the impact study is completed, a new challenge awaits: the implementation of the clinical prediction rule; i.e. widespread acceptance and adoption of the rule in clinical practice (Figure 1)[14]. From all these insights on implementation research, it becomes apparent that possible barriers need to be identified and addressed, preferably before the start of the impact study, to facilitate implementation during the study, and thereafter. True adoption in clinical practice will take years, as implementation will be done in broader but also new patient populations, with new physicians with different and possibly unexpected perceptions on the use of the clinical prediction rule.

Future perspectives and clinical implications

We conclude with three recommendations in order to guide clinicians as well as future researchers on the topic of clinical prediction rules in patients with chest pain.

1) Whether and when should we measure impact? Impact studies generate the most direct answer to the question whether a clinical prediction rule is truly effective in improving patients outcomes or saving costs. However, it is a laborious and costly enterprise. Therefore, less complicated evaluations like validation studies only focusing on the

group of patients of interest (in our case low-risk patients) should be fully exploited before considering an impact study. After that, remaining uncertainties about the exact balance of intended and (unexpected) unintended effects of routine application of the prediction rule and the corresponding guidance in patient management can be solved by performing an impact trial.

2) How should we design an impact study? A key issue in an impact study is the level of standardisation and control in the delivery of the intervention. We advise researchers to anticipate and act on possible barriers for implementation of the intervention even in a pragmatic trial. Researchers should always define minimal criteria on which aspects of their intervention should be standardized. The standardization should focus on the function and process of the intervention, not necessarily the components themselves. The form of the intervention can be tailored to local conditions, which may enhance effectiveness. Modifications to the parallel cluster randomized trial such as the stepped wedge design may be considered. Advantages such as the possibility for within-hospital comparison and opportunity to measure barriers in implementing the prediction rule in all hospitals need to be weighed against the possible disadvantages such as the inflexibility to extend your inclusion period in case of disappointing inclusion rates.

3) What can we conclude on the impact of the HEART score, based on the HEART-Impact trial? The routine use of the HEART score during the initial assessment of chest pain patients at the emergency department was just as safe as usual care. However, the increase in proportion of early discharge and decrease in use of health care resources following the initial assessment was limited. It is likely that with increasing acceptance, confidence and experience with the HEART score the impact on health care resources and costs increases. A possible adjustment of the HEART score to meet the current hesitation or skepticism, namely whether the use of the HEART score is safe (enough), would be to combine the calculation of the HEART score with the recently implemented 1-hour troponin protocol of the revised European guidelines. The additional serial troponin measurement after one hour is likely to further increase the safety of the HEART score as observed in our trial (which used primarily a single measurement), but is still an improvement over the 3-hour serial measurement of troponin currently used in many hospitals. Further research should focus on identifying low-risk patients, since the main barriers to follow the rule are in these patients, and at the same time this is the group were considerable reduction in the use of health care resources can be achieved.

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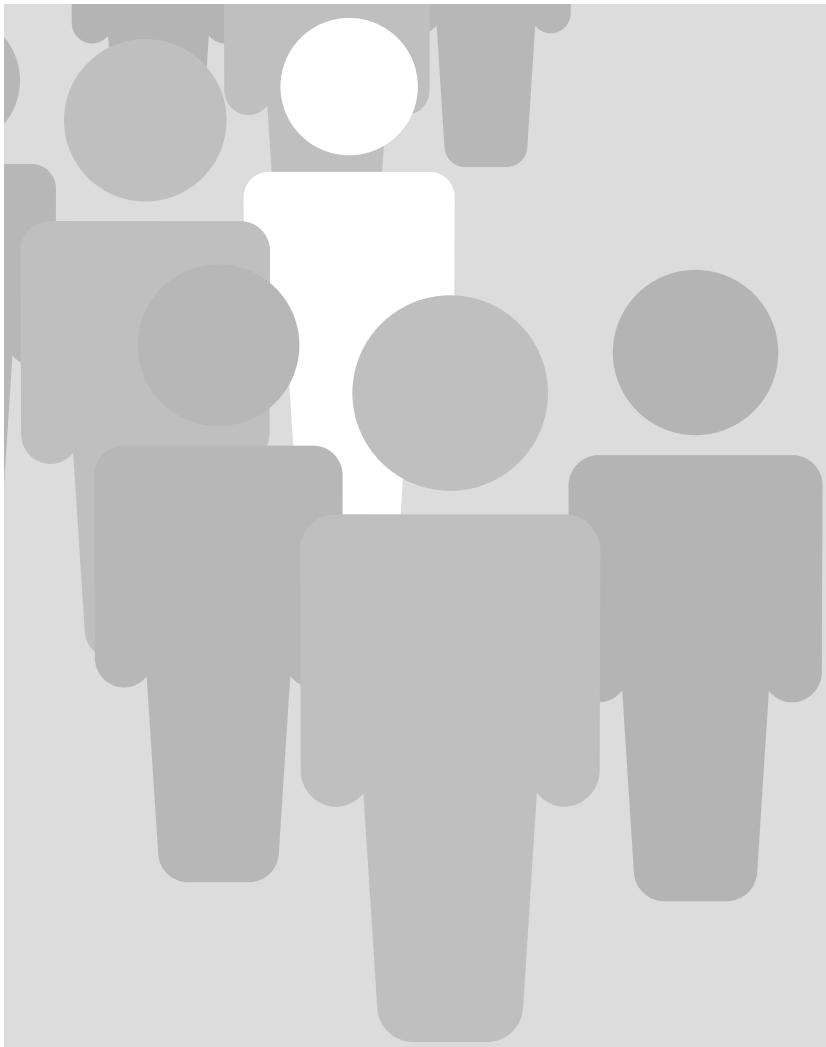
REFERENCES

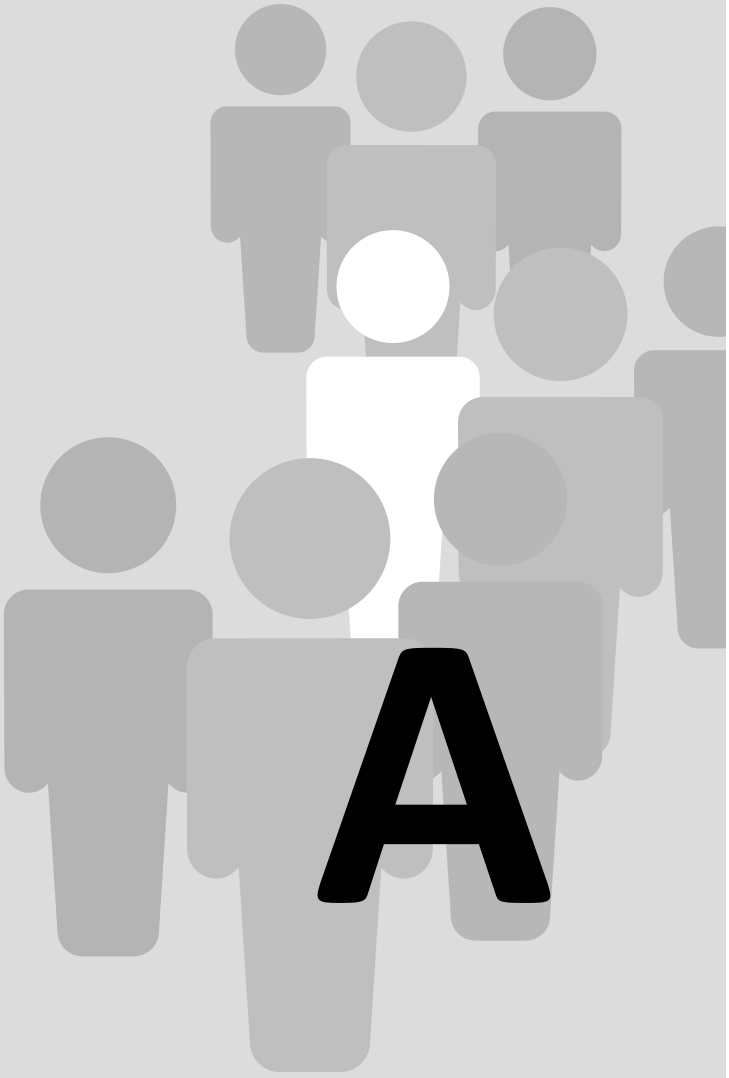
1. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. ESC/EACTS Guidelines on myocardial revascularization. European heart journal. 2014; 35: 2541-2619.
2. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Archives of internal medicine. 2003;163: 2345-53.
3. Body R, Carley S, McDowell G, Pemberton P, Burrows G, Cook G, et al. The Manchester acute coronary syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. Heart. 2014;100(18): 1462-8.
4. Antman EM, Cohen M, Bernink PJLM, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI; a method for prognostication and therapeutic decision making. JAMA. 2000;284:835-42.
5. Christenson J, Innes G, McKnight D, Thompson CR, Wong H, Yu E, et al. A clinical prediction rule for early discharge of patients with chest pain. Annals of emergency medicine. 2006;47: 1-10.
6. Reichlin T, Schindler C, Drexler B, Twerenbold R, Reiter M, Zellweger C, et al. One-hour rule-out and rule-in of acute myocardial infarction using high-sensitivity cardiac troponin T. Arch Intern Med. 2012;172(16):1211-8.
7. Litt HI, Gatsonis C, Snyder B, Singh H, Miller CD, Entrikin DW, et al. CT angiography for safe discharge of patients with possible acute coronary syndromes. N Engl J Med. 2012;366(15):1393-403.
8. Than M, Cullen L, Reid CM, Lim SH, Aldous S, Ardagh MW, et al A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. Lancet. 2011;377(9771):1077-84.
9. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. Neth Heart J 2008;16:191-6.
10. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2015 Aug 29. pii: ehv320.2015.
11. Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. Ann Emerg Med 1999;33:437-47.
12. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. JAMA 2000;284:79-84.
13. Brehaut JC, Stiell IG, Visentin L, Graham ID. Clinical Decision Rules ''in the Real World'': How a Widely Disseminated Rule Is Used in Everyday Practice. Acad Em Med 2005; 12:948–957.
14. Adams ST, Leveson SH. Clinical prediction rules. BMJ 2012;344:d8312
15. Apgar V. A Proposal for a New Method of Evaluation of the Newborn Infant. Current Researches in Anesthesia and Analgesia, July-August, 1953, page 260.
16. Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med. 2000;19(4):453-73.
17. Toll DB, Janssen KJ, Vergouwe Y, Moons KG. Validation, updating and impact of clinical prediction rules: a review. J Clin Epidemiol 2008;61:1085-94.
18. Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. Ann Intern Med 2006;144:201-9.
19. Yealy DM, Auble TE. Choosing between clinical prediction rules. N Engl J Med 2003;349:2553-5.
20. Verma S, Hamilton K, Hawkins HH, Kothari R, Singal B, Buncher R, et al. Clinical application of the Ottawa ankle rules for the use of radiography in acute ankle injuries: an independent site assessment. AJR Am J Roentgenol 1997;169:825-7
21. Hess EP, Thiruganasambandamoorthy V, Wells GA, Erwin P, Jaffe AS, Hollander JE, et al. Diagnostic accuracy of clinical prediction rules to exclude acute coronary syndrome

in the emergency department setting: a systematic review. CJEM. 2008;10(4):373-82.

22. Merlin T, Lehman S, Hiller JE, Ryan P. The "linked evidence approach" to assess medical tests: a critical analysis. Int J Technol Assess Health Care. 2013;29(3):343-50.
23. KNAW (2014). Evaluation of new technology in health care. In need of guidance for relevant evidence. Amsterdam, KNAW.
24. Beard E, Lewis JJ, Copas A, Davey C, Osrin D, Baio G, et al. Stepped wedge randomised controlled trials: systematic review of studies published between 2010 and 2014. Trials. 2015;16:353.
25. Bertens LC, Reitsma JB, van Mourik Y, Lammers JW, Moons KG, Hoes AW, et al. COPD detected with screening: impact on patient management and prognosis. Eur Respir J. 2014;44(6):1571-8.
26. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015;350:h2147
27. Hawe P, Shiell A, Riley T. Complex interventions: how "out of control" can a randomized controlled trial be? BMJ. 2004;328(7455):1561-3.
28. Six AJ, Backus BE, Kingma A, Kaandorp SI. Consumption of diagnostic procedures and other cardiology care in chest pain patients after presentation at the emergency department. Neth Heart J. 2012; 20(12):499-504.
29. Nieuwets A, Poldervaart JM, Reitsma JB, Buitendijk S, Six AJ, Backus BE, et al. Medical consumption compared for TIMI and HEART score in chest pain patients at the emergency department. *Submitted.*
30. Mahler SA, Hiestand BC, Goff DC, Hoekstra JW, Miller CD. Can the HEART Score Safely Reduce Stress Testing and Cardiac Imaging in Patients at Low Risk for Major Adverse Cardiac Events? Crit Pathways in Cardiol 2011;10: 128–133
31. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003; 362: 1225–30.
32. Oxman A, Flottorp S. An overview of strategies to promote implementation of evidence-based health care. In: Silagy C, Haines A,eds. Evidence-based practice in primary care, 2nd edn. London: BMJ books, 2001.
33. Brace-McDonnell SJ, Laing S. When is low-risk chest pain acceptable risk chest pain? Heart. 2014;100(18):1402-3.
34. Christenson J, Innes G, McKnight D, Boychuk B, Grafstein E, Thompson CR, et al. Safety and efficiency of emergency department assessment of chest discomfort. CMAJ 2004;170:1803-7.
35. John RM, Tedrow UB, Koplan BA, Albert CM, Epstein LM, Sweeney MO, et al. Ventricular arrhythmias and sudden cardiac death. Lancet. 2012;380(9852):1520-9.
36. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008;337:a1655.
37. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. BMJ 2013;347:f6753



Appendix



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SUMMARY

In 6% of all patients presenting to the emergency department the reason is chest pain, which results in approximately 200.000 patients in total per year in The Netherlands[1]. A minority of these patients have an acute coronary syndrome (ACS), and need prompt admission and treatment[2]. However, differentiating between ACS and other, mostly non-life-threatening disease, remains a diagnostic dilemma for every physician, since laboratory results and electrocardiography (ECG) can be normal even though an ACS is present. Therefore, current practice is often a defensive one: most chest pain patients are hospitalized for observation and additional testing[3]. This is not only a time-consuming and costly strategy, but also puts many low risk patients for ACS at risk of complications of these diagnostic procedures. This emphasizes the importance of research on the risk stratification of patients presenting with chest pain, in particular the identification of patients at low risk for ACS.

In this thesis we have evaluated and compared several strategies for more efficient management and diagnosis of chest pain patients at the emergency department. These different strategies include the use of a risk score (such as the GRACE score, HEART score or TIMI score), or additional diagnostic tests such as the bicycle stress test or laboratory results (biomarkers).

In **Chapter 2** we performed an additional analysis on the prospective validation cohort of the HEART score and compared the TIMI score and the HEART score in terms of medical consumption. We found that the HEART score identified more patients as low risk compared to the TIMI score (256 vs. 105), with potential savings of €63,657 vs. €14,670. If the HEART score would have guided further management in these patients, it could have led to a reduction in diagnostic procedures and costs. However, in this study the HEART score nor the TIMI score were not actively used in patient management, therefore, our recommendation for future research is to prospectively investigate whether adhering to the HEART score and early discharge of low-risk patients results in lower use of health care resources and actual reductions in costs.

The design of such an impact study is presented in **Chapter 3.** The HEART-Impact trial is a stepped wedge, cluster randomized trial in patients presenting at the emergency department with chest pain in 9 hospitals in the Netherlands. Stepped wedge designs are increasingly used to evaluate the real-life effectiveness of interventions. Each hospital has both a usual care and an intervention period, therefore, outcomes can be compared within and across hospitals. Furthermore, each hospital will experience the new intervention which may enhance participation in case of a promising intervention. We hypothesized that this large

impact trial would generate evidence whether the anticipated benefits of using the HEART score would indeed be achieved in real-life clinical practice.

In **Chapter 4** the findings of the HEART-Impact trial are reported. In this trial we compared "usual care" with "HEART care" in terms of safety, use of medical resources and costs. The HEART care included a calculation of the HEART score in every individual patient and adherence to the recommendation of policy. Our findings were that active use of the HEART score during initial assessment of chest pain patients at the emergency department is just as safe as usual care, since non-inferiority was demonstrated: six-week incidence of major adverse cardiac events (MACE) during HEART care was 1.3% lower than during usual care (upper limit 95% CI: +2.0%). The proportion of early discharge within 4 hours after initial presentation was higher during HEART care (34.4 vs. 30.6%, difference after adjustment for clustering and time steps +0.7%; 95% CI: -10.6 to +11.9%) and decrease in use of health care resources following the initial assessment was small. Differences in health outcomes and costs were limited, although cost-effectiveness was formally demonstrated: the probability that HEART dominates usual care equals 71.0%, and the probability that HEART is cost-effective for a Willingness-to-Pay (WTP) threshold of €20,000/QALY equals 99.4%.

Several risk scores have been developed over the years, and the use of these risk scores has been advocated in all international cardiac guidelines. Therefore, in **Chapter 5** we compared the performance of the HEART score with two other well-known scores, namely the GRACE score and the TIMI score, to predict major adverse cardiac events in a head-to-head manner using the data of HEART impact trial. Our findings were that the HEART score is the most efficient score to use at the emergency department to estimate short-term risk for cardiac events in chest pain patients, since it identified the largest number of patients as low risk, without compromising a fixed level of safety.

An active area of research is the search for novel, high sensitive cardiac biomarkers to improve the early diagnosis of ACS at the emergency department. However, most studies report on the value of a cardiac biomarker alone, without examining the added value on top of already available information from clinical assessment (like history taking) and electrocardiography. In **Chapter 6** we investigated with data from the FAME-ER study the added diagnostic value of novel cardiac biomarkers for diagnosis of ACS on top of current clinical practice (history taking, medical history, risk factors and ECG findings combined in the form of a "clinical model"). We also examined the added value of these markers on top of the current practice of measurement of a high-sensitive troponin T (hs-TnT). When assessing patients with chest pain suspected of ACS, only the marker myoglobin had added diagnostic value beyond clinical symptoms and ECG. However, when combined with hs-cTnT,

it yielded no additional diagnostic value. All other novel biomarkers, namely PlGF, sFlt-1, NT-proBNP, GDF-15 and copeptin, had no added value to the clinical model or hs-cTnT.

A diagnostic test currently most frequently used in patients presenting with chest pain, apart from the ECG and laboratory tests, is the bicycle stress test. In **Chapter 7** we evaluated the diagnostic value of bicycle stress testing. We re-evaluated the executed bicycle stress tests in a part of the study population using data of the previous prospective validation study of the HEART score. On top of risk stratification by the HEART score, bicycle stress testing has only a modest contribution to clinical decision-making. In total, 50% of all tests are non-conclusive, with high rates of false positive tests in all three HEART risk groups. In intermediate-risk patients, negative exercise tests may contribute to the exclusion of disease. Our advice is that clinicians should rather go for sensitive tests, in particular in patients with intermediate HEART scores, and furthermore should refrain from testing with the bicycle exercise test in low risk patients.

In conclusion, the diagnosis of ACS at the emergency department in clinical practice remains difficult and there are several options for the clinical work-up of these patients. Our findings in the HEART-Impact trial indicate that the use of the HEART score is safe, however the limited impact on health care resources also underline the importance to identify possible barriers inhibiting the acceptance of the recommended management in the low-risk HEART group. Based on the results presented in this thesis, we would advise the use of the HEART score in the work-up of chest pain patients in more hospitals. The question whether patients and society truly benefits from the use of the HEART score will hopefully be answered in the coming years, with increasing body of evidence on the HEART score and increasing acceptance and adherence to the score in clinical practice.

REFERENCES

1. http://www.toolkitvtv.nl/inhoud/indicatoren-en-bronnen/zorg/hap-en-seh-ziekenhuis/
2. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. ESC/EACTS Guidelines on myocardial revascularization. European heart journal. 2014; 35: 2541-2619.
3. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart. 2005;91(2):229-30.

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SAMENVATTING

Van alle patiënten die zich presenteren op de Eerste Hulp gaat het in 6% om de klacht “pijn op de borst”. Dit resulteert in ongeveer 200.000 patiënten per jaar in Nederland[1]. Een klein deel van deze patiënten heeft een acuut coronair syndroom (ACS) en behoeft direct opname in het ziekenhuis voor behandeling[2]. Echter, het goed kunnen differentiëren tussen ACS en andere, vaak niet levensbedreigende ziektes, blijft een diagnostisch dilemma voor elke arts. Dit komt onder andere omdat het laboratorium onderzoek en elektrocardiogram (ECG) normaal kunnen zijn, ook wanneer een patiënt wél een ACS heeft. Hierdoor is de huidige klinische praktijk erg defensief ingesteld: de meeste patiënten met pijn op de borst worden opgenomen voor korte of langdurige observatie en ondergaan aanvullende diagnostische onderzoeken[3]. Dit is tijdrovend en gaat gepaard met stijgende gezondheidszorgkosten. Bovendien worden op deze manier veel patiënten die een laag risico op een ACS hebben, blootgesteld aan het risico van complicaties van deze diagnostische (soms invasieve) onderzoeken. Dit benadrukt het belang van wetenschappelijk onderzoek naar de risico stratificatie van patiënten met pijn op de borst, met name zodat deze “laag risico” patiënten geïdentificeerd kunnen worden.

In dit proefschrift hebben we enkele strategieën geëvalueerd en waar mogelijk vergeleken met elkaar, met als doel op de Eerste Hulp de meest efficiënte management van patiënten met pijn op de borst te identificeren. Deze verschillende strategieën zijn: het gebruik van een risico score (zoals de GRACE score, HEART score en TIMI score), of aanvullend onderzoek in de vorm van het uitvoeren van een fietstest of het bepalen van aanvullende laboratoriumwaarden (biomarkers).

In **Hoofdstuk 2** beschrijven we een aanvullende analyse met data van de prospectieve validatie studie van de HEART score. De HEART en TIMI score zijn twee risicoscores, die aan de hand van enkele klinische kenmerken, een patiënt kan inschatten als laag risico op een ACS, of juist een hoog risico. Aan de hand van zo’n risicoscore kan vervolgens het beleid voor de patiënt worden bepaald: moet de patiënt verder nagekeken worden in het ziekenhuis, of kan de patiënt zonder verder onderzoek of observatie veilig naar huis? We vergelijken in Hoofdstuk 2 de TIMI score met de HEART score wat betreft het uitvoeren van diagnostische procedures, opnames en daarmee het maken van medische kosten. In dit hoofdstuk laten we zien dat de HEART score meer patiënten met pijn op de borst identificeert als “laag risico” dan de TIMI score (256 patiënten versus 105 patiënten). Als de HEART score daadwerkelijk gebruikt zou worden voor het verdere beleid van de patiënt met pijn op de borst op de Eerste Hulp, en laag risico patiënten naar huis gestuurd zouden worden zonder verdere observatie, zou dat zodoende tot een reductie van ziekenhuisopnames en

diagnostische procedures kunnen leiden en daarmee tot een reductie in kosten (in deze studie een potentiële kostenreductie van €63,657 met HEART versus €14,670 met TIMI). Echter, in de praktijk wordt de HEART score (of de TIMI score) niet actief gebruikt om het beleid te bepalen in deze patiënten. Het zou dus interessant zijn om te kijken wat er gebeurt, als daadwerkelijk het bijbehorende beleid van de HEART score wordt geïmplementeerd op de Eerste Hulp en dus voor patiënten met laag risico een vroeg ontslag vanaf de eerste Hulp wordt doorgevoerd.

In **Hoofdstuk 3** beschrijven we het studiedesign van de HEART-Impact trial, die precies bovengenoemd doel voor ogen had: observeren wat er gebeurt als je de HEART score implementeert en actief gaat gebruiken in de praktijk bij de beoordeling van patiënten met pijn op de borst. De HEART-Impact trial is een stepped wedge, cluster gerandomiseerde trial, waarin we kijken naar patiënten die zich met pijn op de borst presenteren op de Eerste Hulp van 9 Nederlandse ziekenhuizen. Het stepped wedge design wordt steeds vaker gebruikt om het effect van interventies in de dagelijkse klinische praktijk te evalueren. Elk ziekenhuis begint met een periode van "usual care" oftewel standaard zorg, met daarna een interventie periode (in ons geval de "HEART care"). Hierdoor kunnen uitkomsten worden vergeleken zowel *in* als *tussen* ziekenhuizen. Bovendien krijgt elk ziekenhuis uiteindelijk een interventie periode, wat mogelijk de participatie verhoogt om de nieuwe interventie te implementeren. Onze hypothese is dat deze grote impact trial uiteindelijk bewijs levert of de geanticipeerde voordelen van het gebruik van de HEART score behaald worden in de dagelijkse klinische praktijk.

In **Hoofdstuk 4** beschrijven we vervolgens de resultaten van bovengenoemde HEART-Impact trial. Zoals gezegd vergeleken we in deze trial "usual care" met "HEART care" op het gebied van veiligheid, zorggebruik en kosten. De HEART care bestond uit het uitrekenen van de HEART score in elke individuele patiënt, met daarbij vervolgens navolgen van het aanbevolen beleid. Onze bevindingen van deze trial waren dat actief gebruik van de HEART score tijdens de beoordeling van patiënten met pijn op de borst op de Eerste Hulp net zo veilig is als standaard zorg. We hebben vooraf een limiet voor non-inferiority opgesteld van niet meer dan 3% verschil in het eenzijdige 95% betrouwbaarheidsinterval (BI) voor het optreden van major adverse cardiac events (MACE) binnen 6 weken. De cumulatieve incidentie van major adverse cardiac events (MACE) binnen 6 weken tijdens de HEART care periode bleek 1.3% lager dan tijdens de usual care (bovenste limiet 95% BI: +2.0%). Daarmee hebben we de non-inferiority van de HEART care in deze trial aangetoond. Het percentage van patiënten dat vroeg wordt ontslagen (binnen 4 uur na binnenkomst) vanaf de Eerste hulp was hoger tijdens de HEART care (34.4 vs. 30.6%, verschil na corrigeren voor geclusterde data en tijd +0.7%; 95% BI: -10.6 tot +11.9%). Het zorggebruik volgend op de beoordeling op de

Eerste hulp nam niet duidelijk af in de HEART care periode. Verschillen in uitkomsten en kosten waren er nauwelijks, hoewel kosteneffectiviteit van de HEART score formeel wel kon worden aangetoond: de kans dat HEART care usual care domineert is 71%, en de kans dat HEART care kosteneffectief is bij een Willingness-to-Pay (WTP) limiet van €20,000/QALY is gelijk aan 99%.

Verschillende risicoscores zijn inmiddels ontwikkeld en het gebruik van deze scores wordt aangeraden in alle internationale cardiologische richtlijnen. Daarom hebben we in **Hoofdstuk 5** drie van deze scores head-to-head met elkaar vergeleken, namelijk de GRACE score, de HEART score en de TIMI score. We hebben hiervoor data van de HEART-Impact trial gebruikt, en wilden bekijken welke score het best MACE op korte termijn kon voorspellen. We vonden dat de HEART score de meest efficiënte score is om te gebruiken op de Eerste Hulp, omdat deze het grootste aantal patiënten met pijn op de borst als "laag risico" identificeert, zonder een geaccepteerde uiterste grens van veiligheid (aantal fout-negatieven) te compromitteren.

Een actief gebied van onderzoek is de zoektocht naar nieuwe hoog sensitieve cardiale biomarkers om de vroege diagnose van ACS op de Eerste Hulp te verbeteren en te versnellen. Echter, de meeste studies rapporteren slechts de waarde van een cardiale biomarker op zichzelf, zonder de aanvullende waarde bovenop de reeds aanwezige informatie van klinische evaluatie (zoals de anamnese) en het ECG mee te nemen. In **Hoofdstuk 6** hebben we onderzocht met data van de FAME-ER studie, wat de aanvullende diagnostische waarde van nieuwe cardiale biomarkers was, bovenop de huidige klinische praktijk van anamnese, medische voorgeschiedenis, risicofactoren en het ECG (gecombineerd in een "klinisch model"). We keken ook naar de aanvullende waarde van deze nieuwe biomarkers bovenop de huidige praktijk van de meting van een hoog sensitieve troponine T (hs-TnT). We concludeerden dat bij de beoordeling van patiënten met pijn op de borst, alleen de nieuwe biomarker myoglobine aanvullende diagnostische waarde had bovenop de klinische kenmerken en het ECG. Wanneer we deze biomarker vervolgens combineerden met hs-TnT, was myoglobine niet meer van aanvullende waarde. Alle andere nieuwe biomarkers, te weten PlGF, sFlt-1, NT-proBNP, GDF-15 en copeptine, hadden geen aanvullende waarde bovenop het klinische model of bovenop hs-TnT.

Als laatste hebben we in **Hoofdstuk 7** gekeken naar de waarde van de meest gebruikte diagnostische test, na het ECG en laboratoriumonderzoek, namelijk de fietstest. We gebruikten hiervoor gegevens van een eerdere prospectieve validatie studie van de HEART score en lieten de uitgevoerde fietstesten in een deel van deze populatie van patiënten met pijn op de borst opnieuw beoordelen door twee onafhankelijke cardiologen. We concludeerden dat, wanneer de patiënt reeds een risico stratificatie met de HEART score

heeft ondergaan, de fietstest nog maar weinig bijdraagt aan de klinische besluitvorming. In totaal was 50% van alle fietstesten niet-conclusief, bovendien waren er hoge aantallen van fout-positieve testen in alle drie de HEART risico categorieën. Alleen in de patiënten met een intermediair risico volgens de HEART score, zou een fietstest mogelijk kunnen bijdragen aan het uitsluiten van cardiaal ischemische ziekte. Op basis van deze studie zouden we adviseren dat artsen beter een meer gevoeligere test kunnen gebruiken. Bij patiënten met een laag risico kan het gebruik van een fietstest beter vermeden worden.

Op basis van de gepresenteerde resultaten in dit proefschrift, concluderen wij dat de diagnose van ACS op de Eerste Hulp moeilijk blijft en dat er verschillende manieren zijn om deze patiënten te beoordelen en zo hun risico op ACS in te schatten. Onze bevindingen van de HEART-Impact trial wijzen erop dat het gebruik van de HEART score veilig is, hoewel wij slechts een kleine impact op zorggebruik en kosten konden aantonen. Deze bevindingen laten ook zien dat het belangrijk is om potentiële barrières te identificeren die de acceptatie en gebruik van het aanbevolen beleid van de HEART score tegenhouden, met name bij patiënten in de laag risico categorie. Gebaseerd op de resultaten in dit proefschrift, zouden wij het gebruik van de HEART score als diagnostische beslisregel adviseren bij de beoordeling van patiënten met pijn op de borst. De vraag blijft, of patiënten en ook de maatschappij uiteindelijk echt voordeel ondervinden van het gebruik van de HEART score en het bijbehorende beleid. Mogelijk zullen toekomstige onderzoeken bijdragen aan de body of evidence en tevens bijdragen aan de acceptatie en het naleven van de score in de dagelijkse klinische praktijk.

REFERENTIES

1. http://www.toolkitvtv.nl/inhoud/indicatoren-en-bronnen/zorg/hap-en-seh-ziekenhuis/
2. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. ESC/EACTS Guidelines on myocardial revascularization. European heart journal. 2014; 35: 2541-2619.
3. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart. 2005;91(2):229-30.

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LIST OF PUBLICATIONS

Manuscripts based on the studies presented in this thesis

- **Poldervaart JM,** Röttger E, Dekker MS, Zuithoff NPA, Verheggen PWHM, de Vrey EA, Wildbergh TX, van 't Hof AWJ, Mosterd A, Hoes AW. No added value of novel biomarkers in the diagnostic assessment of patients suspected of acute coronary syndrome. *PLoS One. 2015;10(7):e0132000.*
- **Poldervaart JM**, Reitsma JB, Koffijberg H, Backus BE, Six AJ, Doevendans PA, Hoes AW. The impact of the HEART risk score in the early assessment of patients with acute chest pain: design of a stepped wedge, cluster randomised trial. *BMC Cardiovascular Disorders. 2013;13:77.*
- **Poldervaart JM**, Six AJ, Backus BE, de Beaufort HW, Cramer MJ, Veldkamp RF, Gijs Mast, Buijs EM, Tietge WJ, Groenemeijer BE, Cozijnsen L, Wardeh AJ, den Ruiter HM, Doevendans PA. The predictive value of the exercise ECG for major adverse cardiac events in chest pain patients at the emergency department. *Clin Res Cardiol. 2013;102(4):305-12.*
- **Poldervaart JM,** Reitsma JB, Backus BE, Koffijberg H, Veldkamp RF, Appelman Y, ten Haaf ME, Mannaerts HFJ, van Dantzig JM, van den Heuvel M, el Farissi M, Rensing BJWM, Ernst NMSKJ, Dekker IMC, den Hartog FR, Oosterhof T, Lagerweij GR, Buijs EM, van Hessen MWJ, Landman MAJ, van Kimmenade RRJ, Cozijnsen L, Bucx JJJ, van Ofwegen-Hanekamp CEE, Cramer MJ, Six AJ, Doevendans PA, Hoes AW. Impact of using the HEART score in chest pain patients at the emergency department: a stepped wedge, cluster randomised trial. *Submitted, under review.*
- **Poldervaart JM,** Langedijk M, Backus BE, Dekker IMC, Six AJ, Doevendans PA, Hoes AW, Reitsma JB. Comparison of the performance of the GRACE, HEART and TIMI score to predict acute coronary syndrome in patients presenting with chest pain at the emergency department. *Submitted, under review.*
- Nieuwets A, **Poldervaart JM,** Reitsma JB, Buitendijk S, Six AJ, Backus BE, Doevendans PA, Hoes AW. Comparing the TIMI score and HEART score in chest pain patients at the emergency department: potential impact on medical consumption. *Submitted, under review.*

Other publications

- Engel J, van der Wulp I, **Poldervaart JM,** Reitsma JB, de Bruijne MC, Wagner C. Clinical decision making of cardiologists regarding admission and treatment of suspected unstable angina or non-ST-elevation myocardial infarction patients: a study protocol of a clinical vignette study. BMJ Open. 2015;5(4):e006441.

- Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, Veldkamp RF, Wardeh AJ, Tio R, Braam R, Monnink SH, van Tooren R, Mast TP, van den Akker F, Cramer MJ, **Poldervaart JM,** Hoes AW, Doevendans PA. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol. 2013;168(3):2153-8.
- Engel J, **Poldervaart JM,** van der Wulp I, Reitsma JB, de Bruijne MC, Bunge, JJH, Cramer MJ, Tietge W, Uijlings R, Wagner C. Selecting patients with non ST-elevation acute coronary syndrome for coronary angiography: a nationwide clinical vignette study in the Netherlands. *Submitted, under review.*

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DANKWOORD

Allereerst wil ik me wenden tot mijn promotieteam.

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CURRICULUM VITAE

Judith Maria Poldervaart was born on January 21, 1986 in Hilvarenbeek, the Netherlands. After cum laude graduation from secondary school Stedelijk Gymnasium Breda in 2004, she studied medicine at the Utrecht University, the Netherlands. As part of this study, she was involved in a research project at the department of Cardiology of the University Medical Center Utrecht under supervision of Dr. Jacob Six and Dr. Barbra Backus. This research project focused on the added value of bicycle exercise testing in chest pain patients and can be found in this thesis. In 2011 she started working as a resident at the department of Cardiology of the Rivierenland Ziekenhuis in Tiel. Thereafter, she started working as a PhD student on the HEART-Impact trial as described in this thesis at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, under supervision of Prof. dr. Arno Hoes, Prof. dr. Pieter Doevendans, Dr. Hans Reitsma and Dr. Jacob Six. She received her Qualification for Academic Teaching (Basis Kwalificatie Onderwijs (BKO)) of the Utrecht University in 2013. Furthermore, she combined her PhD research project with the Postgraduate Master of Clinical Epidemiology at the Utrecht University for which she obtained her degree in 2015. She currently has a postdoctoral research position at the Julius Center within the department of primary care and in the future aims to combine her research work with a general practice training.