Pre-hospital risk stratification in suspected Non ST-elevation acute coronary syndrome

PRE-HOSPITAL RISK STRATIFICATION IN SUSPECTED NON ST-ELEVATION ACUTE CORONARY SYNDROME

Dominique N. van Dongen

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Promotor	Prof. dr. A.W.J. van 't Hof
Copromotores	Dr. J.P. Ottervanger (Isala Zwolle) Dr. R. Slingerland (Isala Zwolle)
Beoordelingscommissie	Prof. dr. J.W.L. Cals (voorzitter) Prof. dr. O. Bekers Prof. dr. H.J.G.M. Crijns Prof. dr. J.P.S. Henriques (University of Amsterdam) Dr. J. Meeder (VieCurie Medical Center, Noord Limburg)

"Above all else, guard your heart, for everything you do flows from it"

Proverbs 4:23

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General introduction and outline

GENERAL INTRODUCTION

Chest pain & ambulance transports Chest pain is one of the most frequent symptoms among patients contacting the emergency medical services and a common reason for ambulance transport to the hospital. Although the concern is that the cause of complaints is a myocardial infarction, the majority of patients are discharged without a cardiac diagnosis (figure 1) and with a high survival rate[1]. Early risk prediction seems to be important for downgrading and thus cost saving in selected chest pain patients, and for fast treatment in high-risk patients.

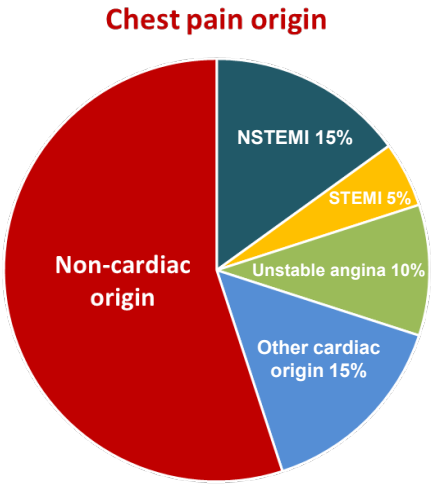

Figure 1 Distribution of chest pain origin

Non-ST-elevation acute coronary syndrome Acute Coronary Syndrome (ACS) refers to a spectrum of conditions characterized by acute myocardial ischemia, which results from reduced blood flow in one or more coronary arteries. Patients with ACS can be distinguished into three clinical manifestations, according to the appearance of the electrocardiogram (ECG): ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina (UA). The second and third group are often more difficult to identify and need extra testing like blood analysis and physical examination.

ACS is a potentially life-threatening cardiac condition that requires prompt diagnosis and treatment. Patients with STEMI are rapidly transferred to the hospital for urgent coronary artery catheterization and, if needed, revascularization. Patients with

suspected NSTE-ACS are usually rapidly transferred to an emergency department for clinical evaluation and monitoring. A targeted history and physical examination, repeated ECG recording and blood samples for analysis of troponin and other markers of cardiac necrosis are cornerstones of the diagnostic process.

Current practice: Hospital risk stratification Suspected NSTE-ACS is a common reason for emergency department presentation. First, it is important to differentiate between real ACS and other (cardiac) diagnoses. Second, in those with real ACS rapid risk stratification is crucial to efficiently distinguish low-risk patients that can be discharged on short term, and high-risk patients that benefit from acute treatment. Over the years, several protocols to diagnose NSTE-ACS based on troponin assessment are developed[2]. In addition, risk stratification protocols in patients with proven ACS are available to determine how fast coronary artery catheterization should be performed.

However, in 80% of patients presenting to the emergency department with chest pain, complaints are of non-cardiac and non-acutely threatening origin[2]. Until now, there are no specific recommendations on further diagnostics, treatment and time to discharge in this large group of low-risk patients.

Clinical prediction rules Many strategies have been developed to distinguish low- and high-risk patients[3]. Beside troponin protocols, clinical prediction rules were developed which are designed to fasten and increase convergence in the decision making process in the hospital[4]. Clinical prediction rules consist of variables including history, physical examination and often basic diagnostic tests, such as laboratory tests.

One of these prediction rules is the HEART score. This is a risk score from 0 to 10 points, which combines troponin assessment, clinical parameters and ECG findings to stratify patients with suspected NSTE-ACS to low, intermediate or high risk for major adverse cardiac events (MACE) (Figure 2). The HEART score has been extensively validated in different countries and settings[4–6] and is nowadays internationally used on emergency departments.

Pre-hospital risk stratification To date, risk assessment in suspected NSTE-ACS patients is mainly performed in the hospital. However, since point of care devices (POC) were developed[7], troponin can also be measured outside the hospital. Subsequently, pre-hospital risk stratification in suspected NSTE-ACS is also possible if paramedics are capable in distinguishing low- and high-risk patients. Theoretically, the HEART score can be performed by paramedics in the pre-hospital setting. However, although the HEART score is extensively validated in the hospital, the implementation of a pre-hospital

HEART score performed by paramedics has never been investigated before. This is remarkable since most patients are first seen by paramedics. Also, the possible impact on safety (false negatives), costs and diagnostics have never been assessed before. The key questions are whether pre-hospital risk assessment by paramedics is feasible for identification of low-risk patients, high-risk patients and whether this can reduce health care costs without an increase in the occurrence of MACE.

Main objectives of this thesis This thesis focusses on pre-hospital risk stratification in patients with suspected NSTE-ACS. The objectives of this thesis are firstly to assess feasibility and safety in identifying low-risk patients by pre-hospital HEART score assessment by paramedics, secondly to assess the impact on healthcare utilization and lastly to assess whether patients at high-risk for early revascularization can be identified pre-hospitally.

Figure 2 HEART score

HEART score			
History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥ 65 years	2	
	> 45 and <65 years	1	
	≤ 45 years	0	
Risk factors*	≥ 3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin	≥ 3x normal limit	2	
	1-2 x normal limit	1	
	Normal limit or lower	0	
		Total	

* Risk factors: Hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, BMI > 30kg/m^2

ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; PM = pacemaker.

OUTLINE OF THE THESIS

The aim of this thesis was to assess whether pre-hospital risk stratification in patients with suspected NSTE-ACS is feasible, safe and cost efficient.

Chapter 2 contains the first phase of the Famous Triage study in which we investigated whether a pre-hospital HEART score performed by paramedics is feasible and reliable in predicting the incidence of MACE within 45 days in patients with suspected NSTE-ACS. In this phase troponin was measured in the hospital from pre-hospital derived blood. In **Chapter 3** phase 2 of the Famous Triage study is presented. In this observational phase a complete pre-hospital HEART score including point-of care troponin was assessed by paramedics. **Chapter 4** shows that POC troponin assessment within the HEART score has important added value. In **Chapter 5** we compared the HEART score using POC troponin with the HEART score using high sensitive troponin. **Chapter 6** Compares pre-hospital HEART score assessment performed by paramedics with hospital HEART score assessment performed by physicians. In **Chapter 7** we assessed healthcare utilization in low-risk patients. **Chapter 8** shows that pre-hospital elevated point-of-care troponin is a strong predictor for early revascularization and is superior to the HEART score for prediction of revascularization in patients with suspected NSTE-ACS. Finally, in **Chapter 9** the rationale and design for the third, implementation, phase of Famous Triage is presented.

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2

A prospective study on pre-hospital risk stratification using the HEART score in suspected NSTE-ACS

Rudolf T. Tolsma, MSc, Dominique N. van Dongen, MD, Marion J. Fokker ing., Erik Badings, MD PhD, Aize van der Sluis, MD, Robbert J. Slingerland, PhD, Arnoud W.J. van 't Hof MD PhD, Jan Paul Ottervanger, MD PhD

Submitted

ABSTRACT

Background Previous studies demonstrated the feasibility and safety of the HEART score for risk stratification by physicians in patients visiting the emergency department with suspected NSTE-ACS. This study investigated whether pre-hospital risk stratification by paramedics using the HEART score is feasible.

Methods In a total of 600 consecutive patients with suspected NSTE-ACS the HEAR components of the HEART score were prospectively assessed by paramedics. Blood samples were collected at time of inclusion and troponin assessment was performed in the hospital. Endpoint was occurrence of MACE within 30 days of inclusion.

Results Mean age was 63 years, 58% was male. A total of 140 patients (23%) were classified as low, 341 (57%) as intermediate and 119 (20%) as high-risk patients. Occurrence of MACE within 30 days was 2.9%, 19% and 45%, respectively ($p < 0.001$). There were no deaths in the low-risk group. AUC of the pre-hospital HEART score for predicting MACE was 0.77 (95% CI 0.725 – 0.813).

Conclusion A pre-hospital assessed HEART score in patients with suspected NSTE-ACS is feasible and accurate in identifying patients at low- and high risk for MACE. If troponin assessment is possible in the ambulance, risk stratification of patients with suspected NSTE-ACS can possibly be performed pre-hospitally in the future.

INTRODUCTION

Early risk stratification in patients with suspected NSTE-ACS is important to assess which patient needs fast diagnostics and treatment, but also to identify low-risk patients that can be discharged at short term.

Previous studies demonstrated the ability of risk stratification in suspected NSTE-ACS[1–4] and several risk stratification tools are developed including the HEART score (Figure 1).[5,6] This is an easily assessable tool which has shown to be adequate in distinguishing low- and high-risk groups.[7]

Until now, all risk stratification tools were validated for hospital use. However, since most patients with suspected NSTE-ACS are initially seen by paramedics, pre-hospital risk stratification could enhance decisions about transportation and treatment. Evidence based tools for pre-hospital risk stratification in patients with suspected NSTE-ACS are therefore of importance. We investigated whether risk stratification by paramedics using the HEART score is feasible in a pre-hospital setting.

Figure 1 HEART score

HEART score			
History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥ 65 years	2	
	> 45 and <65 years	1	
	≤ 45 years	0	
Risk factors*	≥ 3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin	≥ 3x normal limit	2	
	1-2 x normal limit	1	
	Normal limit or lower	0	
		Total	

* Risk factors: Hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, BMI > 30kg/m²

ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; PM = pacemaker.

METHODS

Study design and population The aim of this first phase of the Famous Triage Study (Fast Assessment and Management of Chest Pain without ST-elevation in the Pre-hospital Gateway)[8,9] is to investigate whether pre-hospital risk stratification by paramedics using the HEART score in suspected NSTE-ACS patients is feasible and accurate.

This is a prospective observational cohort study including 600 consecutive patients from Isala and Deventer hospital which are tertiary and secondary care hospitals in the Netherlands. The inclusion criteria were out-of-hospital patients visited by an ambulance with a pre-hospital suspicion of NSTE-ACS at first medical contact, with age ≥ 18 years. The exclusion criteria were pregnancy, comatose state, cognitive impairment, shock, cardiac asthma, sustained ventricular tachyarrhythmia, end stage renal disease, an obvious non-cardiac cause for chest complaints or a strong suspicion of aortic dissection or pulmonary embolism. A design paper was previously published.[8] A total of 33 ambulances were involved in the study. The study was registered in the Dutch Trial Register [http://www.trialregister.nl]: trial number 4205. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee.

HEART score assessment Paramedics obtained the HEAR elements of the HEART score during the first medical contact. The HEART score is shown in figure 1. Each element (History, ECG, age, risk factors, troponin) is scored with 0, 1 or 2 points. The sum of these elements results in a total HEART score between 0 – 10.

History comprises presence of suspicious complaints of the patient (for example middle- or left sided, heavy chest pain, radiation, relief of symptoms by sublingual nitrates, nausea, vomiting and/or sweating). Paramedics evaluated the ECG without help of automatic ECG judgment programs. Risk factors were assessed by evaluation of medication use and a questionnaire about presence of diabetes mellitus, current or recent smoking, hypertension, hypercholesterolemia, family history of coronary artery disease, obesity (body mass index BMI ≥ 30), or a history of significant atherosclerosis (coronary revascularization, myocardial infarction, ischemic stroke and/or peripheral arterial disease). The HEAR components were recorded in a digital patient dossier and retracted and anonymized for analysis.

Troponin assessment Paramedics collected venous blood from an intravenous cannula at time of inclusion. After admission at the ED, the blood samples were analyzed at the clinical chemistry laboratory by a Cobas 8000/6000 system of Roche Diagnostics with an hs-cTnT Modular. The limit of blank was 0.003 ng/mL. Inaccuracy corresponded to

a 10% coefficient of variation at the 99th percentile upper reference limit (URL) of the reference population. When the hs-cTnT value exceeded the 99th percentile, URL 0.014 ng/mL, it was considered elevated. 0 Points were granted when the hs-cTnT was ≤ 0.014 ng/mL. 1 point was granted for hs-cTnT of 0.014 – 0.042 and 2 points were granted for hs-cTnT ≥ 0.042.

Outcome and diagnostic adjudication The outcome was occurrence of MACE within 30 days of inclusion. MACE was defined as acute coronary syndrome comprising STEMI, NSTEMI and unstable angina; revascularization by either PCI or CABG or death by all cause. Endpoint assessments were performed by two independent adjudicators by medical record studies using current ESC guidelines. In case of disagreement a third independent adjudicator was consulted. When there was no in-hospital follow up at 30 days, patients were contacted by telephone or via the patients general practitioner to identify MACE within 30 days.

Statistical analysis Statistical analysis was performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were reported by frequencies and percentages. Continuous variables were tested for normality of distribution. For the comparison of normally distributed variables a t test was used to compare means, for non-normally distributed variables a non-parametric variant (Mann - Whitney U test) was used. A chi square test was performed to test differences of categorical variables. To evaluate the sensitivity and specificity of the pre-hospital HEART scores for MACE, a receiver operator characteristics (ROC) analysis was performed and area under the curve with 95% confidence interval was assessed. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

From June 2013 until December 2014 a total of 600 consecutive patients with suspected non-STEMI were included in the analysis. There was no missing follow up.

Baseline clinical characteristics are shown in table 1. 349 (58%) Were male, mean age was 63.1 (± 14.6) years. A total of 140 patients (23%) were classified as low, 341 (57%) as intermediate and 119 (20%) as high risk for MACE. 14 (10%) Low-risk patients were admitted to the hospital from the emergency department versus 70 (59%) in the high-risk patient group.

Within 30 days of inclusion, a total number of 122 patients (20%) experienced MACE (table 3). 112 (19%) patients experienced ACS, 44 (7.3%) underwent PCI, 36 (6.0%) received a CABG and 4 patients (0.7%) died. Incidence of MACE was higher in males (OR 2.26 95% CI 1.46 – 3.51).

Table 1 Baseline clinical characteristics at hospital presentation of 600 patients with suspected NSTE-ACS, stratified into three risk groups by paramedics

	Total Group N= 600	Low-risk N=140	Intermediate risk N=341	High-risk N=119
Male, n (%)	349 (58)	81 (58)	190 (56)	78 (66)
Mean age, years (SD)	63,1 (15)	52.0 (13)	63.5 (13)	75.2 (10)
Hypertension , n (%)	266 (44)	42 (30)	160 (47)	64 (54)
Hypercholesterolemia, n (%)	168 (28)	31 (22)	98 (29)	39 (33)
Diabetes, n (%)	96 (16)	7 (5.0)	54 (16)	35 (29)
Smoking, n (%)	133 (22)	36 (26)	87 (26)	10 (8.4)
Family history, n (%)	192 (32)	51 (36)	117 (34)	24 (20)
Obesity, n (%)	33 (5.5)	6 (4.3)	23 (6.7)	4 (3.4)
History CAD, n (%)	86 (14)	6 (4.3)	48 (14)	32 (27)
Previous MI, n (%)	111 (18.5)	10 (7.1)	64 (19)	37 (31)
Previous revascularization, n (%)	124 (21)	8 (5.7)	73 (21)	43 (36)
Previous stroke	18 (3.0)	1 (0.7)	11 (3.2)	6 (5.0)
Troponin T > 0,014 ng/mL, n (%)	168 (28)	4 (2.9)	73 (21)	91 (76)
Hospital admission, n (%)	169 (28)	14 (10)	85 (25)	70 (59)

Several baseline variables were significantly associated with MACE (table 2), including the amount of hs-cTnT release, the risk group according the HEART score, previous myocardial infarction, history of coronary artery disease and previous revascularization. Low-risk HEART score was a significantly negative predictor of MACE (OR 0.09 95% CI 0.03 – 0.24). High-risk HEART score was a significant predictor of MACE (OR 5.05 95% CI 3.24 – 7.86).

Distribution of MACE is shown in table 3. There was a strong association between HEART score category and incidence of MACE, corresponding with a significant difference in MACE within 30 days of 2.9%, 19% and 45% respectively. Also, the pre-hospital HEART score was a strong predictor of the individual components of MACE. There were no deaths in the low-risk group. Receiver operator characteristics (ROC) analysis of the HEART score as predictor for MACE within 30 days showed an area under the curve (AUC) of 0.77 (95% 0.73 – 0.81, $p < 0.001$) (Figure 2).

Table 2 Predictors of MACE

	Total	MACE	No MACE	P value*
Population	600	122 (20)	478 (80)	<0.01
Male	349 (58)	89 (25)	260 (75)	<0.01
Age ≤45	64 (11)	4 (6.3)	60 (94)	0.01
Age 45-65	256 (43)	52 (20)	204 (80)	<0.01
Age ≥ 65	280 (47)	66 (24)	214 (76)	<0.01
Elevated Troponin	168 (28)	78 (46)	90 (54)	<0.01
HEART >6	119 (20)	54 (45)	65 (55)	<0.01
HEART >3	460 (77)	118 (26)	342 (74)	<0.01
Hypertension	266 (44)	60 (23)	206 (77)	0.23
Hypercholesterolemia	168 (28)	39 (23)	129 (77)	0.27
Diabetes	96 (16)	25 (26)	71 (74)	0.13
Smoking	133 (22)	30 (23)	103 (77)	0.47
Family history CAD	192 (32)	46 (24)	146 (76)	0.13
Obesity	33 (5.5)	4 (12)	29 (88)	0.23
History CAD	86 (14)	26 (30)	60 (70)	0.01
Previous MI	111 (19)	36 (32)	75 (68)	<0.01
Previous revascularization	124 (21)	37 (30)	87 (70)	<0.01
Previous stroke	18 (3.0)	17 (94)	1 (5.5)	0.11

* p-value for difference between Patients with and without MACE

Table 3 MACE within 30 days follow up in 600 patients with suspected NSTE-ACS, stratified into low, intermediate and high risk by paramedics

	Total Group N= 600	Low-risk N=140 (23%)	Intermediate risk N=341 (57%)	High-risk N=119 (20%)	P value*
MACE, n(%)	122 (20)	4 (2.9)	64 (19)	54 (45)	<0.01
ACS, n(%)	112 (19)	4 (2.9)	58 (17)	50 (42)	<0.01
PCI, n(%)	44 (7.3)	3 (2.1)	24 (7.0)	17 (14)	<0.01
CABG, n(%)	36 (6.0)	1 (0.7)	18 (5.3)	17 (14)	<0.01
Death, n(%)	4 (0.7)	0 (0)	1 (0.3)	3 (2.5)	0.02

MACE: major adverse cardiac events; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting.
*p-value for difference between three risk groups.

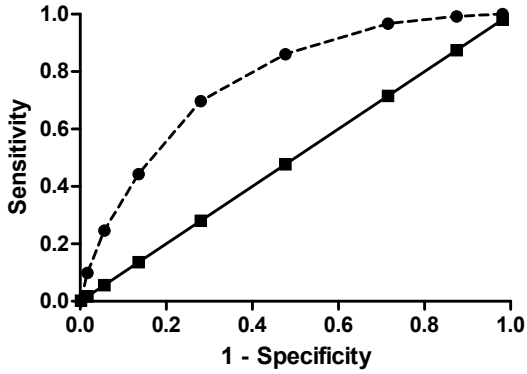

Figure 2 Receiver operator characteristics (ROC) analysis, of the HEART score for 30 days major adverse cardiac events. This shows an area under the curve of 0.77 (95% 0.73 – 0.81, p < 0.001)

DISCUSSION

In this study it was shown that in patients with suspected NSTE-ACS, risk stratification by paramedics using the HEART score, is accurate in predicting MACE within 30 days. These findings provide an opportunity to improve decision making for paramedics treating patients with suspected NSTE-ACS.

Compared with a recent study which investigated the hospital acquired HEART score[10], the distribution across the three different risk categories differs in our previous study (e.g. 39% were low-risk group vs. 23% in this study). Differences in interpretation can occur in the H(istory), E(CG) and R(isk factor) elements of the HEART score. Results of the risk factors scoring are comparable with our previous study, so it seems that paramedics tend to score the history and ECG more suspicious than physicians at the ED.

With 4 patients (2.9%) in the low-risk group developing a MACE in the follow up period, this study reported a higher percentage of MACE than other HEART score studies[5,6,10] 10 other patients from the low-risk group were admitted to the hospital. Possible explanations are that the paramedics did not get additional training in how to perform the HEART score. This was the first phase of the study in which the paramedics had to get familiar with the HEART score. Besides that, in this phase there was no consequence for decision making with the results of the HEART score. It is therefore possible that the score was filled in less precisely by the paramedics. Moreover, the results were based on one single troponin measurement. Particularly

in patients with short duration of complaints, troponin was possibly not yet abnormal. These patients might be stratified in a higher risk group after a second measurement, a few hours later.

Clinical implications This is the first study in which risk stratification using the HEART score was performed pre-hospitally by paramedics. The next step is to investigate whether a complete HEART score assessment by paramedics is feasible. This is possible with point-of-care (POC) devices for the measurement of Troponin. Also, additional training of paramedics how to perform the HEART score is important.

In the Netherlands there are over 1.2 million ambulance deployments per year. In practice, about 25% of all deployments encounter cardiology cases.[11] Paramedics work according to National Ambulance Protocols. The protocol for patients with suspected NSTE-ACS mainly focuses on pre-hospital medication administration. There is no standardized format for further risk stratification. Whether a patient should be transferred is decided by the paramedic after clinical assessment.

Further research is needed to investigate whether use of a complete pre-hospital HEART score, including pre-hospital troponin measurement is feasible. This may further optimize pre-hospital management of chest pain patients through rapidly identification of low-risk patients who possibly do not need hospital transfers and rapid identification of high-risk patient leading to a shorter time to treatment.

As stated previously, in patients with a short duration of complaints the results of troponin measurement can lead to false negative results. Therefore, we advise a second troponin measurement in case of short duration of the complaints. This is also recommended by the current ESC guidelines.[12]

Limitations This study has several limitations. The sample size of this study is insufficient to perform subgroup analyses. Also, in this study troponin measurement was performed in the hospital. Therefore, we cannot conclude whether a true complete pre-hospital HEART score is feasible for predicting MACE. This study was performed in 2 hospitals, to make the results stronger it should be validated in other hospitals. Ambulance care in the Netherlands is organized differently from most other countries which might make the results less generalizable for other countries. Finally, paramedics were not trained in performing the HEART score. We expect that additional training can result in more reliable HEART score results.

CONCLUSION

A pre-hospital HEART score assessed by paramedics in suspected NSTE-ACS is feasible for prediction of MACE within 30 days. This can change the pre-hospital pathway and it can make logistics of patients with suspected NSTE-ACS more efficient.

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Pre-hospital risk assessment in suspected non-ST-elevation acute coronary syndrome: a prospective observational study

Dominique N. van Dongen, Rudolf T. Tolsma, Marion J. Fokkert, Erik A. Badings, Aize van der Sluis, Robbert J. Slingerland, Arnoud W.J. van 't Hof, Jan Paul Ottervanger

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ABSTRACT

Background Pre-hospital risk stratification of non-ST-elevation Acute Coronary Syndrome (NSTE-ACS) by the complete HEART score has not yet been assessed. We investigated whether pre-hospital risk stratification of patients with suspected NSTE-ACS using the HEART score is accurate in predicting major adverse cardiac events (MACE).

Methods This is a prospective observational study, including 700 patients with suspected NSTE-ACS. Risk stratification was performed by ambulance paramedics, using the HEART score; low-risk was defined as HEART score ≤ 3. Primary endpoint was occurrence of MACE within 45 days after inclusion. Secondary endpoint was myocardial infarction or death.

Results A total of 172 patients (24.6%) were stratified as low risk and 528 patients (75.4%) as intermediate to high-risk. Mean age was 53.9 years in the low-risk group and 66.7 years in the intermediate to high-risk group ($p < 0.001$), 50% was male in the low-risk group versus 60% in the intermediate to high-risk group ($p = 0.026$). MACE occurred in 5 patients in the low-risk group (2.9%) and in 111 (21.0%) patients at intermediate or high risk ($p < 0.001$). There were no deaths in the low-risk group and the occurrence of acute myocardial infarction in this group was 1.2%. In the high-risk group 6 patients died (1.1%) and 76 patients had myocardial infarction (14.4%).

Conclusions In suspected NSTE-ACS, pre-hospital risk stratification by ambulance paramedics, including troponin measurement, is accurate in differentiating between low and intermediate-high risk. Future studies should investigate whether transport of low-risk patients to the hospital can be avoided, and whether high-risk patients benefit of immediate transfer to a hospital with early coronary angiography possibilities.

INTRODUCTION

While in ST elevation Myocardial Infarction (STEMI), management is clear and well defined, in patients with suspected NSTE-ACS, early risk stratification is crucial to define the type of early management.[1,2] Several methods have been validated for risk stratification in (suspected) NSTE-ACS, including the HEART score, TIMI, GRACE and PURSUIT.[3–6] In current daily practice, risk stratification is performed after hospital admission, but ambulance paramedics, from here forth referred to as paramedics, probably have the opportunity for earlier stratification.[7,8] However, until now, it has never been demonstrated that pre-hospital risk stratification, including troponin assessment, by paramedics can accurately discriminate patients with suspected NSTE-ACS into low, intermediate and high-risk. In this part of the Famous Triage study we investigated whether early risk stratification by paramedics using the HEART score, including pre-hospital troponin assessment, is feasible and accurate in predicting the incidence of Major Adverse Cardiac Events (MACE) within 45 days after admission.[7] The aim of our study was therefore to assess whether pre-hospital risk stratification is accurate in patients with suspected NSTE-ACS.

METHODS

Study design and population This prospective observational cohort study, the second phase of the Famous Triage project[7,8], was performed between January 2016 and July 2017, and included patients from Isala and Deventer hospitals which are tertiary and secondary care hospitals in The Netherlands. The study involved 33 emergency medical services (EMS) vehicles from two regional ambulance services (RAV IJsselland and Witte Kruis ambulancezorg) staffed by approximately 110 paramedics. The aim was to determine the accuracy of risk stratification by paramedics in patients with suspected NSTE-ACS. The study was conducted according to the principles of the Declaration of Helsinki and did not require an informed consent procedure for study participation because the medical ethics committee approved the study as observational and considered all study activities to fit within the boundaries of usual care. The inclusion criteria were out-of-hospital patients visited by an ambulance with a pre-hospital suspicion of NSTE-ACS at first medical contact, with age ≥ 18 years. The exclusion criteria were pregnancy, comatose state, cognitive impairment, shock, cardiac asthma, sustained ventricular tachyarrhythmia, end stage renal disease, an obvious non-cardiac cause for chest complaints or a strong suspicion of aortic dissection or pulmonary embolism.

Sample size calculation Based on the results of phase 1 of our study[8], it was estimated that 700 patients would be sufficient to demonstrate whether early risk stratification by paramedics using the HEART score, including pre-hospital troponin assessment, in suspected NSTE-ACS is accurate in predicting the incidence of Major Adverse Cardiac Events (MACE) within 45 days after admission in low-risk patients. It was assumed that prevalence of low-risk patients would be 20 – 35%, with MACE 1 – 3%. Because it was expected that 20% of patients would have missing data or loss of follow up, the total sample size was estimated to be 875 participants.

Routine clinical assessment Before the start of this study, all paramedics were trained in assessing the HEART score. Prior to inclusion, all patients underwent routine assessment including a brief history, monitoring of vital signs (blood pressure, heart rate, pulse oximetry), 12-lead ECG and intravenous access, according to local EMS protocols. Paramedics assessed eligibility for inclusion based on this routine assessment and the above mentioned in- and exclusion criteria. In case of uncertainty the paramedics were able to contact a cardiologist and sent the ECG digitally. The HEART score elements and scoring system are shown in Appendix A in the Supplementary Material online. HEART components were determined and registered including a troponin point of care test. Patients were then presented to the emergency cardiac care unit and further treatment was given according to usual care protocols. Risk factors and medication use necessary for pre-hospital HEART assessment were collected by the paramedics by standard questionnaires. Low-risk was defined as HEART score ≤ 3.

Troponin assays A cardiac troponin T assay was performed on site using the Roche CARDIAC POC troponin T test on the cobas h 232 POC system with a limit of detection of 40 – 2000 ng/L. The POC cTnT assay was validated previously and showed excellent concordance with the calibration and reference high sensitive troponin laboratory method.[9] The cobas h232 POC device is able to work properly in a temperature range from 18 to 32 °C, a relative humidity of 10–85 % (no condensation) and maximum altitude of 4300 m. The POC testing strips are sustainable for 7 days after removal from the refrigerator. Blood was derived after insertion of a venous line. It was not derived by venapunction. POC test results were available in 8 – 12 min. Taking measurements during driving was avoided. A troponin value below 40ng/L was scored 0 points in the HEART score and a troponin value exceeding 40 ng/L was considered elevated and scored 2 points. In hospital, a Hs-cTnT was assessed at the clinical chemistry laboratory using the hs-cTnT Modular and Cobas 8000 system of Roche Diagnostics, Manheim Germany, with a limit of detection of 3 ng/L and inaccuracy corresponding to a 10% coefficient of variation at the 99th percentile upper reference limit (URL) of the reference population. A hs-cTnT value exceeding the 99th percentile URL (14 ng/L) was considered elevated.

Diagnostic adjudication Adjudication of the final diagnosis was performed by applying current guidelines and the third universal definition of myocardial infarction[1,10,11]. The first 12-lead ECG obtained at the emergency department was evaluated and scored for endpoint adjudication according Minnesota criteria.[12] Acute coronary syndrome was defined as STEMI, which was determined by ECG judgement, non-STEMI and unstable angina. Non-STEMI diagnosis was made when the in-hospital cardiac high sensitive troponin (hs-cTnT) value was elevated, meaning a value exceeding the 99th percentile URL (14 ng/L) with a significant delta as well as a clinical setting including possible ECG characteristics consistent with myocardial ischemia. Unstable angina was diagnosed when there was a clinical setting consistent with myocardial ischemia and cardiac troponin was normal or above the 99th percentile URL without a significant delta. All other patients were diagnosed with stable angina, non-cardiac chest pain or cardiac but non-coronary disease (e.g. tachyarrhythmias, heart failure). A percutaneous coronary intervention (PCI) was defined as a percutaneous strategy of therapeutic intracoronary balloon dilatation and/or stent placement. Coronary artery bypass grafting (CABG) was defined as a surgical procedure of coronary artery grafting to bypass a coronary stenosis.

Follow up and clinical endpoints The primary outcome was the occurrence of MACE within 45 days after inclusion. The original follow up duration according the design paper was extended, because the HEART score was previously validated to predict MACE within six weeks[13] and to be able to compare results with the most recent HEART implementation study.[14] An additional analysis of MACE within 30 days was performed. MACE was defined as acute coronary syndrome (ACS), death by all cause, PCI or CABG. Secondary outcome was the occurrence of myocardial infarction or death within 45 days. To compare results with a multinational HEART validation study[3], a post-hoc analysis was performed in which only urgent revascularization (considered revascularization during hospitalization) was adjudicated as MACE. Medical records were studied to identify MACE. When there was no in-hospital follow up after 45 days, patients were contacted by telephone or via the patient's general practitioner. Information regarding death was obtained from the national registry on mortality.

Patient involvement The medical ethical committee included a representative of patients. Patient priorities were considered, but no patients were involved in development of the research protocol. However, the protocol was funded by the Isala Research Fund and approved by a committee which included two participants of the patient council of Isala hospital.

Statistical analysis Statistical analysis was performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR). Categorical variables were reported by frequencies and percentages and compared with the Chi square test, and a Fisher exact test if appropriate. Variables were tested for normality of distribution. For the comparison of normally distributed variables a *t* test was used to compare means; for non-normally distributed variables a non-parametric variant (Mann-Whitney U) was used. The difference in the occurrence of MACE during 45 days follow up between the low and intermediate-high risk groups was assessed by the Kaplan-Meier method using the log-rank test. To demonstrate the independent predictive value of intermediate-high risk HEART score on MACE, multivariable analyses were performed, using logistic regression model. To evaluate the sensitivity and specificity of the pre-hospital HEART score on 45 days MACE, a receiver operator characteristics (ROC) analysis was performed. Analyses of area under the curve (AUC) with confidence interval (CI) analysis were performed. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

From January 2016 to July 2017 a total of 823 patients were deemed eligible by paramedics. A complete HEART score was not available in 120 patients (14.6%) due to missing troponin results (87 patients) or incomplete registration of HEART scores (41 patients). Main reasons for the absence of a troponin result were device error, unavailability of testing strips or inability to obtain blood. Three patients with a complete HEART score were lost to follow up.

A total of 700 patients (85.1%) with a complete HEART score were included in the analysis. Mean age of the total group was 63.6 years, 57.3% were male. Prevalence of hypercholesterolemia was 39.3%, hypertension 53.1%, and a history of prior PCI 25%. A total of 172 patients (24.6%) were stratified as low risk, 528 patients (75.4%) as intermediate-high-risk. Baseline characteristics in the two risk groups are shown in Table 1. The intermediate-high risk patients were older, more often male, had a significantly higher prevalence of cardiovascular risk factors and significantly more often prior atherosclerotic diseases. The median duration between start of symptoms and troponin measurement in our study was 150 minutes (IQR 65 – 443 min).

The cumulative incidence of MACE within 45 days in the study group was 16.6%. Differences between patients with and without MACE are summarized in Table 2. Increasing age, male gender, diabetes and a history of myocardial infarction were positively associated with MACE. Additionally, the HEART score was positively correlated with MACE at 45 days.

Table 1 Patient Characteristics

Characteristics	HEART ≤ 3 n = 172 (24.6%)	HEART > 3 n = 528 (75.4%)	P value
Demographics			
Mean age, y (SD)	53.9 (12.2)	66.7 (12.6)	< .001
Male, n (%)	86 (50.0)	315 (59.7)	0.026
Cardiac risk factors, No. (%)			
Diabetes Mellitus	9 (5.3)	111 (21.7)	< .001
Body mass index ≥ 30kg/m²	33 (27.7)	107 (24.7)	0.502
Hypercholesterolemia*	46 (27.4)	229 (44.9)	< .001
Hypertension^	62 (36.5)	310 (60.4)	< .001
Positive family history	77 (45.8)	247 (48.2)	0.588
Current smoker	44 (26.2)	112 (22.0)	0.264
History of cardiovascular disease, No. (%)			
AMI	13 (7.6)	137 (25.9)	< .001
PCI	13 (7.6)	162 (30.7)	< .001
CABG	2 (1.2)	64 (12.1)	< .001
TIA/Stroke	2 (1.2)	41 (7.8)	0.002
Peripheral artery disease	2 (1.2)	29 (5.5)	0.017

CAD = coronary artery disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack.
* Hypercholesterolemia refers to patients receiving lipid-lowering therapy; ^Hypertension refers to patients receiving blood pressure medication

Differences in the components of MACE between the low-risk and the intermediate-high risk group are summarized in table 3. MACE incidence was significantly higher in the intermediate-high risk group (21%) as compared to the low-risk group (2.9%).

Table 2 Comparison of patients with MACE and without MACE

	MACE n = 116	No MACE n = 584	P value
Demographics			
Mean age (SD), y	68.1 (12.8)	62.7 (13.6)	<.001
Male, n (%)	88 (75.9)	313 (53.6)	<.001
HEART ≤ 3	5 (4.3)	167 (28.6)	<.001
HEART > 3	111 (95.7)	417 (71.4)	
Cardiac risk factors, No. (%)			
Diabetes Mellitus	26 (22.4)	87 (14.9)	0.044
Body mass index ≥ 30kg/m²	27 (26.2)	113 (25.2)	0.826
Hypercholesterolemia*	61 (53.7)	214 (37.9)	0.002
Hypertension^	66 (57.9)	306 (53.8)	0.421
Positive family history	47 (41.2)	277 (48.9)	0.133
Current smoker	30 (26.5)	126 (22.3)	0.332
History of cardiovascular disease, No. (%)			
AMI	34 (29.3)	116 (19.9)	0.024
PCI	42 (36.2)	133 (22.8)	0.002
CABG	14 (12.1)	52 (8.9)	0.287
TIA/Stroke	11 (9.5)	32 (5.5)	0.095
Peripheral artery disease	11 (9.5)	20 (3.4)	0.004

CAD = coronary artery disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack.

* Hypercholesterolemia refers to patients receiving lipid-lowering therapy; ^Hypertension refers to patients receiving blood pressure medication

Survival curves according MACE in the low and the intermediate-high risk group are depicted in Figure 1. In 73 patients with MACE, but negative point of care (POC) troponin, median time between onset of complaints and POC troponin assessment was 85 minutes (IQR 23 – 210), which was significantly shorter than in the other 43 patients with MACE and positive POC troponin (240 minutes, IQR 60 – 875, p = 0.001). There was no difference in MACE incidence between the two hospitals (p = 0.594). To evaluate the performance of the HEART score in predicting MACE within 45 days a ROC analysis was performed (Figure 2). This showed an AUC of 0.74 (95% CI 0.69 – 0.79, p <0.001). Considering the secondary endpoint of this study, the incidence of myocardial infarction was 1.2% in the low-risk group (without deaths) versus 14.4% in the intermediate-high risk group (six deaths), p < 0.001. For this secondary endpoint, the AUC was 0.75 (95% CI 0.70 – 0.81, p < 0.001).

Table 3 45 days incidence of different components of MACE in patients with HEART ≤ 3 and HEART > 3

	HEART ≤ 3 n = 172	HEART > 3 n = 528	P value
MACE, No. (%)			
Patients with MACE	5 (2.9)	111 (21.0)	< .001
Patients with MACE including only urgent revascularization	5 (2.9)	102 (19.3)	< .001
MACE components			
Death	0 (0.0)	6 (1.1)	0.160
Total cardiac ischemia	4 (2.3)	96 (18.2)	< .001
Unstable angina	2 (1.2)	19 (3.6)	
Non-STEMI	2 (1.2)	73 (13.8)	
STEMI	0 (0.0)	4 (0.8)	
Coronary revascularization	4 (2.3)	89 (16.8)	< .001

MACE = major adverse cardiac events; Non-STEMI = Non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction

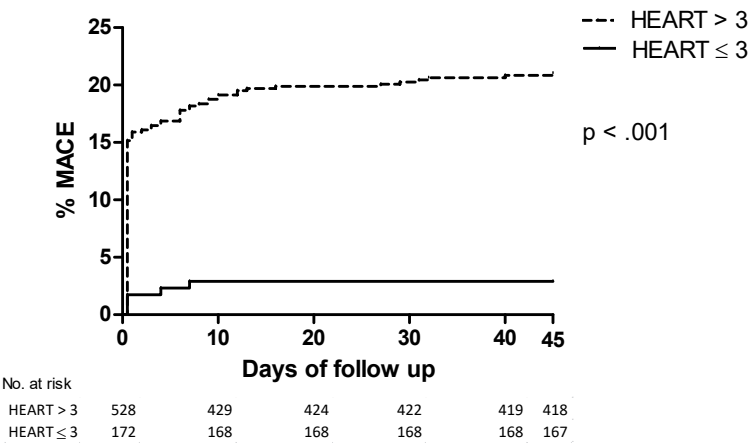

Figure 1 Kaplan Meier curves of MACE (death, ACS, revascularization) of patients in the low-risk group (HEART ≤ 3) and intermediate-high risk group (HEART > 3).

Results of the analysis of MACE only including urgent revascularization (considered revascularization during hospitalization) are shown in Table 3. There was no difference in MACE incidence in the low-risk group, but the incidence of MACE in the intermediate-high risk group was significantly lower (p = 0.004). MACE after 30 days of follow up instead of 45 days follow up was 2.9% in the low-risk group, compared to 20.3% in the intermediate-high risk group (p < 0.001).

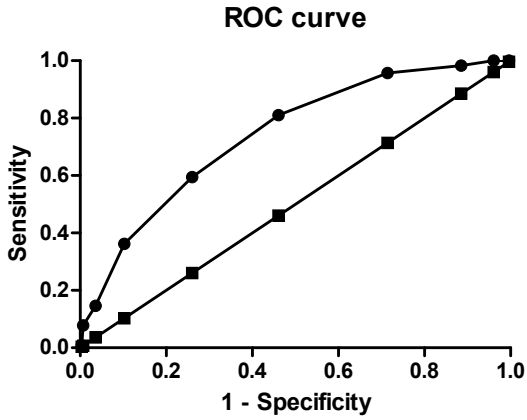

Figure 2 Receiver operator characteristics (ROC) analysis, of the HEART score for 45 days major adverse cardiac events. This showed an area under the curve (AUC) of 0.74 (95% confidence interval 0.69 – 0.79, p <.001).

Of the five patients in the low-risk group that were adjudicated with MACE within 45 days, four patients were adjudicated NSTE-ACS. One patient received elective revascularization. In retrospect, three patients were misclassified as low risk because risk factors were not scored correctly. The two other patients were included shortly after start of complaints. They had elevated troponin results after repeated troponin measurement during hospital admission. A table with patient characteristics, reasons for misclassification and hs-cTnT values after admission is added to Appendix B in the Supplementary Material online. In sensitivity analysis using hospital hs-cTnT to calculate the HEART score instead of POC troponin one of five low-risk patients with MACE would have been classified as intermediate risk. Consequently, MACE would have occurred in four patients (2.3%). A sensitivity analysis taking into account the three missing follow up patients (two homeless without contact information, one asylum seeker) and hypothesizing that all had a MACE within 45 days, would result in 4.0% MACE in the low-risk group.

Most common discharge diagnoses in the low-risk group were non-specified thoracic complaints (n = 155, 90%) and stable angina (n = 9, 5%). Other diagnoses were atrial fibrillation, pancreatitis, cholecystitis, pericarditis (all n = 1).

Survival analyses were performed according to MACE at 45 days. Both age (odds ratio (OR) 1.03, 95% CI 1.02 – 1.05) and male gender (OR 2.72, 95% CI 1.73 – 4.29) were significantly associated with MACE. Diabetes was not statistically significant associated with MACE (OR 1.54, 95% 0.95 – 2.50). The total HEART score was a significant predictor

of MACE (OR 1.71, 95% CI 1.49 – 1.96). Intermediate-high risk HEART score was also a significant predictor of MACE (OR 8.89, 95% CI 3.57 – 22.17). Multivariable analyses did not change these results. Adjusted for gender, patients in the intermediate-high risk group had still a significant increased risk of MACE at 45 days (OR 8.45, 95% CI 3.38 – 21.13).

DISCUSSION

This prospective observational study demonstrated that in suspected NSTE-ACS, risk stratification by paramedics using the HEART score including troponin assessment, is accurate in distinguishing low and intermediate-high risk patients for MACE. These results confirm previous suggestions for pre-hospital risk assessment, based on proven diagnostic accuracy in the hospital setting.[3,15–21] This is the first study in which risk stratification, including troponin assessment, is completely carried out by paramedics, in the pre-hospital setting.

The proportion of intermediate-high risk patients in our study was larger than in previous Dutch studies using the HEART score at the emergency department.[8,14,15] In part, this could be explained by a higher prevalence of risk factors and previous cardiac events in our study. Our population may be different, or classification of risk factors by paramedics in the acute situation may be different from classification by medical doctors during hospitalization. However, previously it was shown that the HEART score has a very strong overall inter-operator agreement between physicians and nurses with varying experience and education.[22] Troponin measurement was performed earlier after symptom onset in our study, but this would result in more often normal troponin scores, and can therefore not explain the higher proportion of intermediate-high HEART scores in our study.

The cumulative incidence of MACE in the low-risk group (2.9%) is higher than in previous in-hospital HEART studies in which MACE incidence ranged from 0.99% to 2.0%.[3,14,15,17,20] There are a few remarks considering this finding. The first involves the definition of MACE. In our study, all PCI's or CABGs (both urgent and elective) were adjudicated as endpoint, whereas in the international validation study, only urgent revascularization was considered as MACE.[3] If in that study elective revascularization is added, the amount of low-risk patients experiencing an endpoint was 3.5% in the low-risk group and 22.2% in the intermediate-high risk group which is in fact even higher than the prevalence of MACE in our study.

Second, cardiac ischemia was defined in a different way in previous HEART studies. In the prospective multicenter study of Backus *et. al.*,[15] only non-STEMI and STEMI were considered as MACE. In our study, also unstable angina was adjudicated as MACE which is in line with a recent implementation study of Poldervaart *et al.*,[14] In that study, the prevalence of MACE in the low-risk group was 2.0%.

In retrospect, of the five patients in the low-risk group with MACE, three patients were misclassified because of incorrect risk scoring by paramedics. In the two other patients troponin would have been elevated if a second POC troponin measurement was performed. This is an important finding which must be taken into account in future implementation studies.

Strengths Our study had several strengths. First, it is the first prospective study, assessing implementation of a complete HEART score in the pre-hospital setting. Second, including patients of two large hospitals covering rural as well as more densely populated urban areas of the Netherlands makes the results well generalizable. Finally, we had a complete follow up in almost all patients (99.6%).

Limitations Our study had some noteworthy limitations. Despite the simplicity of the HEART score, a complete score was absent in 120 patients (14.6%), mostly due to a missing troponin measurement (72.5%). The main cause of the absence of troponin measurement was attributed to device errors of the cobas h 232 POC system. Another cause was the inability to obtain blood. According to local protocols, currently only a peripheral venous cannula is administered by paramedics, and venous blood sampling is not routine practice. Including venous blood sampling by paramedics in routine clinical practice, or the development of troponin measurement with capillary blood sampling, can increase the ability to assess a complete HEART score. Moreover, newly developed POC systems might be more user-friendly and may have fewer errors. A general limitation concerned the single troponin measurement. Since also our results showed that troponin measurement was more often false negative when measured shortly after symptom onset, a second measurement could have classified low-risk patients even more accurately. Also, a potential selection bias cannot be fully excluded, since a complete HEART score was not available in 120 patients (14.6%). Another limitation is that we did not compare our results with other risk calculation methods, like TIMI or GRACE. The sample size of our study was too small to perform analyses of subgroups. Last, a point of concern may be time delay by paramedics in collecting blood samples. However, Stengaard *et. al.*, 2013[23] have established that paramedics spend an extra two min extra on scene when POC troponin is assessed.

Clinical implications of our study This observational study showed that risk stratification in suspected NSTE-ACS by paramedics using the HEART score was accurate in pre-hospital distinction between low risk and intermediate-high risk for MACE within 45 days.

Prior to implementation of this risk assessment tool, further research on real-life implementation should be performed. It should be demonstrated what is the best therapeutic strategy for the individual patient. Also, before the decision can be made of whether low-risk patients can stay at home, paramedics should receive additional training in HEART score assessment to prevent misclassification and a second troponin measurement should be performed to identify patients with non-STEMI who present shortly after onset of complaints. The development of POC troponin tests with higher sensitivity may avoid the need of a second HEART assessment in the future.

An important question is what is an acceptable MACE rate in the low-risk group, both for the hospital (patients may go home) and pre-hospital (patient may stay at home) setting. In primary care, a recent study showed that in patients with chest pain which was retrospectively adjudicated cardiac and life-threatening, 18.2% of patients were not referred to a hospital, and 40.9% of patients were referred to a specialist but not the same day of presentation.[24] A recent study of the same study group, showed a false negative rate for general practitioners clinical judgement for ACS of 2.6%.[25] Nevertheless, avoidance of unnecessary hospital transfers will reduce use of healthcare resources and future studies should assess which patient can stay at home with acceptable risk.[26] High-risk patients can be rapidly identified by the HEART score and possibly directly transferred to an intervention center. For example, occlusion of the circumflex artery can be easily missed electrocardiographically, but if these patients are classified as high-risk, fast transport to a PCI center may be beneficial.[27] Whether a HEART score should be performed in the first place remains to the discretion of the paramedic. Also importantly, paramedics need to evaluate the indication for hospital examination in case of suspicion of a potentially dangerous alternative cause of symptoms. Last, in the future, when patients will stay at home, it is important that their general practitioner is informed and patients are instructed by the paramedic to contact their general practitioner for investigation of the cause of their symptoms, particularly when symptoms persist.

CONCLUSION

This prospective observational study shows that in suspected NSTE-ACS, pre-hospital HEART score assessment including troponin measurement by paramedics is feasible and accurate in differentiating between low and intermediate-high risk. Further research on real-life implementation is needed before pre-hospital management can be changed

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SUPPLEMENTAL MATERIAL

Appendix A HEART score (Figure 2 introduction section)

Appendix B Patient characteristics of five patients with MACE in the low-risk group

	Age, years	Sex	Pre-hospital HEART	Hospital Hs-cTnT (ng/L)	Discharge diagnosis	Revas-culari-zation	Time to MACE (days)	Remarks
1	64	F	H1 E0 A1 R1 T0 3	5	Unstable angina	+	8	Patient already on waiting list for CABG
2	50	M	H0 E1 A1 R0 T0 2	9	NSTEMI	-	0	No significant stenosis. MINOCA
3	44	M	H1 E1 A1 R1 T0 3	11	Unstable angina	+	1	
4	63	M	H1 E1 A1 R0 T0 3	30	Stable angina	+	5	Patient had known coronary artery disease, hypercholesterolaemia and family risk
5	42	M	H2 E0 A0 R0 T0 2	12	NSTEMI	+	0	Smoker

MACE= major adverse cardiac events; NSTEMI = Non-ST-segment elevation myocardial infarction; CABG = coronary artery bypass grafting; MINOCA = myocardial infarction with non-obstructive coronary arteries

4

Value of pre-hospital troponin assessment in suspected non-ST-elevation acute coronary syndrome

Dominique N. van Dongen, Marion J. Fokkert, Rudolf T. Tolsma,
Erik A. Badings, Aize van der Sluis, Robbert J. Slingerland,
Arnoud W.J. van 't Hof MD, Jan Paul Ottervanger

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ABSTRACT

Introduction There is an increasing awareness that pre-hospital risk stratification in patients with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS) is important. The HEART score accurately identifies patients at low risk and is nowadays fully assessable outside the hospital after the development of point-of-care (POC) troponin tests. However, the added value of the troponin component to the pre-hospital HEART score has not yet been assessed.

Methods This is a prospective cohort study including 700 patients with suspected NSTE-ACS in which pre-hospital risk stratification using the HEART score was performed by paramedics. Low risk was defined as HEAR or HEART score ≤3. Troponin was measured by a POC troponin T Test device (Roche Cobas h232). Troponin <40 ng/l scored 0 point, troponin 40 ng/l scored 2 points. Primary endpoint was major adverse cardiac events (MACE) within 45 days after inclusion.

Results Mean HEAR score was 4.5 ± 1.6, mean HEART score was 4.7 ± 1.7. Using the HEAR score, a total of 183 patients (26%) were stratified as low risk, whereas using the HEART score, 172 patients (25%) were stratified as low risk ($p = 0.001$). In both low-risk groups, there were no deaths within 45 days. Using HEAR, MACE occurred in 13 patients (7%) in the low-risk group, whereas using HEART, MACE occurred in 5 patients in the low-risk group (3%, $p < 0.001$). The use of HEART (Area under the curve 0.74) obtained a higher predictive value compared to HEAR (Area under the curve 0.65, $p < 0.001$) for MACE.

Conclusion in patients with suspected NSTE-ACS, the pre-hospital troponin component of the HEART score has important added predictive value.

INTRODUCTION

Early risk assessment in patients with suspected non-ST elevation acute coronary syndrome (NSTE-ACS) provides valuable information about prognosis and facilitates treatment decisions.[1] Currently, there is an increasing awareness that pre-hospital risk stratification is feasible.[2,3] Several studies have shown the predictive value of clinical variables, electrocardiogram (ECG) abnormalities and troponin.[4–11] The HEART score combines clinical parameters, ECG and troponin to stratify patients with suspected NSTE-ACS to low, intermediate and high risk for major adverse cardiac events (MACE).[12] A number of studies have validated the HEART score.[12–14] However, although troponin measurement is nowadays obtainable in the ambulance and has already proven to be of prognostic value,[15–17] the added value of the pre-hospital measured troponin component in the HEART score has not yet been demonstrated. We investigated whether a pre-hospital troponin measurement has added value to a pre-hospital assessed HEART score in predicting the incidence of MACE within 45 days in patients with suspected NSTE-ACS.

METHODS

This prospective observational cohort study, the second phase of the Famous Triage project,[2,3] was performed between January 2016 and July 2017. Patients from Isala and Deventer hospital were included which are tertiary and secondary care hospitals in the Netherlands. The study involved 33 emergency medical services vehicles from 2 regional ambulance services (RAV IJsselland and Witte Kruis ambulancezorg) staffed by approximately 110 paramedics. The original aim of the second phase of the Famous Triage project was to determine the accuracy of risk stratification by paramedics in patients with suspected NSTE-ACS. The aim of the current study was to investigate whether a pre-hospital troponin measurement has added value to the pre-hospital assessed HEART score in predicting the incidence of MACE within 45 days in patients with suspected NSTE-ACS. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The medical ethical committee included a representative of patients. Patient priorities were considered, but no patients were involved in the development of the research protocol. However, the protocol was funded by the Isala Research Fund and approved by a committee which included 2 participants of the patient council of Isala hospital.

The inclusion criteria were out-of-hospital patients with age ≥ 18 years, visited by an ambulance with a pre-hospital suspicion of NSTE-ACS at first medical contact. The exclusion criteria were pregnancy, comatose state, cognitive impairment, shock, cardiac asthma, sustained ventricular tachyarrhythmia, end-stage renal disease, an obvious non-cardiac cause for chest complaints or a strong suspicion of aortic dissection or pulmonary embolism. A design paper was previously published.[3] The study was registered in the Dutch Trial Register [http://www.trialregister.nl]: trial number 4205.

Before the start of this study, all paramedics were trained in HEART score assessment, including point-of care (POC) troponin measurement. Preceding inclusion, all patients underwent routine assessment including a brief history, monitoring of vital signs (blood pressure, heart rate, pulse oximetry), 12-lead ECG and intravenous access, according to local emergency medicine service protocols.

Figure 1 HEART score

HEART score			
History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥ 65 years	2	
	> 45 and <65 years	1	
	≤ 45 years	0	
Risk factors*	≥ 3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin°	≥ 3x normal limit	2	
	1-2 x normal limit	1	
	Normal limit or lower	0	
		Total	

* Risk factors: Hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, BMI > 30kg/m²

° POC troponin below 40ng/L was scored 0, values exceeding 40 ng/L scored 2 points. Hospital troponin was scored according this figure.

ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; PM = pacemaker.

The HEART score is shown in figure 1. ECG analysis was conducted without use of a computer interpretation program. In case of uncertainty, the paramedics were able to contact a cardiologist and sent the ECG digitally. Risk factors were collected by standard questionnaires and by evaluation of medication use. Blood was derived after insertion of a venous line. It was not derived by venapunction. A cardiac troponin T (TnT) assay was performed on site using the Roche CARDIAC POC TnT test on the cobas h 232 POC system with a limit of detection of 40 to 2000 ng/L. The POC TnT assay was validated previously and showed excellent concordance with the calibration and reference high sensitive troponin (hs-TnT) laboratory method.[18] The device is able to work properly in a temperature range from 18°C to 32 °C, a relative humidity of 10% to 85% (no condensation) and maximum altitude of 4300 meter. The POC testing strips are sustainable for 7 days after removal from the refrigerator. POC test results are available in 8 to 12 minutes. Measurements during driving were avoided. A troponin value below 40 ng/l scored 0 point in the HEART score and a troponin value exceeding 40 ng/l was considered elevated and scored 2 points. Since the limit of detection of the POC test is 40 ng/l, it was not possible to score 1 point for troponin which originally is given when hs-TnT is elevated 1 to 3 times the upper reference limit.

After HEART assessment and registration by the paramedic, patients were presented to the emergency cardiac care unit and further treatment was given according to usual care protocols. Low-risk was defined as a HEART or HEAR score ≤ 3.

Adjudication of the final diagnosis was performed by applying current guidelines and the third universal definition of myocardial infarction.[1,19,20] Cardiac ischemia was defined as ST-segment elevation myocardial infarction (STEMI), which was determined by ECG judgement, non-ST-segment elevation myocardial infarction (non-STEMI) and unstable angina. Non-STEMI diagnosis was made when the in-hospital hs-TnT value was above the 99th percentile upper reference limit (0.014 ng/ml) with a significant delta and ECG judgement and a clinical setting consistent with myocardial ischemia. Unstable angina was diagnosed as a clinical setting consistent with myocardial ischemia and normal hs-TnT or above the 99th percentile upper reference limit without a significant delta. All other patients were diagnosed with stable angina, noncardiac chest pain or cardiac but noncoronary disease (e.g., tachyarrhythmias and heart failure). A percutaneous coronary intervention (PCI) was defined as a percutaneous strategy of therapeutic intracoronary balloon dilatation and/or stent placement. A coronary artery bypass surgery was defined as a surgical procedure of coronary artery.

The primary outcome was the occurrence of MACE within 45 days after inclusion. The original follow up duration of 30 days according the design paper was extended, because the HEART score was previously validated to predict MACE within 6 weeks[21] and to be able to compare results with the most recent HEART implementation study.[14] MACE was defined as cardiac ischemia; death by all cause, PCI or coronary artery bypass surgery. To identify MACE, medical record studies were performed. When there was no in-hospital follow up after 45 days, patients were contacted by telephone or through the patient's general practitioner. Information regarding death was obtained from the national registry on mortality.

Statistical analysis was performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp., Armonk, New York). Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR). Categorical variables were reported by frequencies and percentages and were compared with chi-square test. Variables were tested for normality of distribution. For the comparison of normally distributed variables a t-test was used to compare means, for non-normally distributed variables a non-parametric variant (Mann-Whitney U test) was used. Multivariable analyses were not performed because variables were already incorporated in the HEART score. To evaluate the sensitivity and specificity of the pre-hospital HEART and HEAR scores on 45 days MACE, a receiver operator characteristics (ROC) analysis was performed. Analyses of area under the curve (AUC) with confidence interval (CI) analysis were performed. A p value of ≤ 0.05 was considered statistically significant.

RESULTS

From January 2016 to July 2017, a total of 823 patients were considered eligible by paramedics. A complete HEART score was not available in 120 patients (15%) due to missing troponin results (87 patients) and/or incomplete registration of HEART scores (41 patients). Main reasons for the absence of a troponin result were device error, unavailability of testing strips or inability to obtain blood. A total of 3 patients with a complete HEART score were lost to follow up. 700 patients (83%) with a complete HEART score were included in the analysis. Mean age of the total group was 63.6 years, 57% were male. Prevalence of hypercholesterolemia was 39%, hypertension 53%, and 25% of patients had a history of previous PCI. The median duration between the start of symptoms and troponin measurement was 150 minutes (IQR 65 to 435 minutes).

Mean HEAR score was 4.5 ±1.6. Baseline characteristics in the 2 risk groups are shown in Table 1. Based on the HEAR score, a total of 183 patients (26.1%) were stratified as low risk and 517 patients (74%) as intermediate to high risk.

Table 1 Patient Characteristics of patients with HEAR ≤ 3 and HEAR >3

Variable	HEAR ≤ 3 (n = 183)	HEAR > 3 (n = 517)	P value
Age (years)	54.04 (± 12)	66.93 (± 12)	< 0.01
Men (%)	95 (52%)	306 (59%)	0.087
Diabetes Mellitus	10 (6%)	110 (22%)	< 0.001
Body mass index ≥ 30kg/m2	36 (28%)	104 (25%)	0.448
Hypercholesterolemia*	51 (29%)	224 (45%)	< 0.001
Hypertension^	66 (37%)	306 (61%)	< 0.001
Positive family history of CAD	78 (44%)	246 (50%)	0.186
Current smoker	48 (27%)	108 (22%)	0.148
Previous AMI	14 (8%)	136 (26%)	< 0.001
Previous PCI	14 (8%)	161 (31%)	< 0.001
Previous CABG	2 (1%)	64 (12%)	< 0.001
Previous TIA/Stroke	2 (1%)	41 (8%)	0.001
Previous Peripheral artery disease	2 (1%)	29 (6%)	0.011

Values are n (%) or mean ± SD.

CAD = coronary artery disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack.

* Hypercholesterolemia refers to patients receiving lipid-lowering therapy ; ^Hypertension refers to patients receiving blood pressure medication

Baseline characteristics of patients with and without elevated troponin are shown in Table 2. Previous PCI, diabetes mellitus, peripheral artery disease and higher age were predictors of an elevated troponin.

Mean HEART score was 4.7 ±1.7. Baseline characteristics in the 2 risk groups are shown in Table 3. Based on the HEART score, a total of 172 patients (25%) were stratified as low risk, and 528 patients (75%) as intermediate to high risk. The intermediate- to high-risk group according to the HEART score contained significantly more males, whereas there was no significant difference in gender according to the HEAR score.

A total of 116 (17%) patients were diagnosed with MACE within 45 days after inclusion, 100 patients (86% of patients with MACE) were diagnosed with acute coronary syndrome, 93 patients (80%) received coronary revascularization, 6 patients (1%) died. Differences between patients with and without MACE are summarized in Table 4. Using HEAR, 13 patients (7%) in the low-risk group experienced MACE. Using HEART, MACE occurred in 5 patients (3%, p <0.001) in the low-risk group. Death occurred in neither the low-risk group according HEAR nor according HEART. The AUC's and corresponding ROC-curves for the HEAR and HEART score for patients with MACE were compared

(Figure 2). Compared with HEAR (AUC 0.65, CI 0.60 to 0.71), the use of HEART obtained a higher predictive value, (AUC 0.74, CI 0.69 to 0.79, p <0.001) for MACE. The AUC for a pre-hospital elevated POC troponin alone was 0.67 (CI 0.60 to 0.73).

Table 2 Patient Characteristics of patients with normal versus elevated troponin

Variable	Troponin Elevated		P value
	No (n = 631)	Yes (n=69)	
Age (years)	63 (±13)	70 (±15)	< 0.001
Men (%)	356 (56%)	45 (65%)	0.161
Diabetes Mellitus	100 (16%)	20 (30%)	0.004
Body mass index ≥ 30kg/m2	122 (25%)	18 (30%)	0.430
Hypercholesterolemia*	250 (41%)	25 (39%)	0.717
Hypertension^	340 (55)	32 (49%)	0.373
Positive family history of CAD	303 (50%)	21 (33%)	0.01
Current smoker	137 (22%)	19 (30%)	0.185
Previous AMI	129 (20%)	21 (30%)	0.055
Previous PCI	151 (24%)	24 (35%)	0.048
Previous CABG	59 (9%)	7 (10%)	0.830
Previous TIA/Stroke	37 (6%)	6 (9%)	0.352
Previous Peripheral artery disease	23 (4%)	8 (12%)	0.002
MACE, n (%)	73 (12%)	43 (62%)	< 0.001
HEAR ≤ 3	171 (27%)	12 (17%)	0.081
HEAR > 3	460 (73%)	57 (83%)	
HEART ≤ 3	171 (27%)	1 (1%)	<0.001
HEART > 3	460 (73%)	68 (99%)	

Values are n (%) or mean ± SD.

CAD = coronary artery disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack; MACE = major adverse cardiac events.

* Hypercholesterolemia refers to patients receiving lipid-lowering therapy ; ^Hypertension refers to patients receiving blood pressure medication

Both HEAR and HEART scores were significant predictors of MACE (odds ratio [OR] 1.45, 95% CI 1.26 to 1.67; OR 1.71, 95% CI 1.49 to 1.96, respectively). Additionally, intermediate-high-risk HEAR score and intermediate-high risk HEART score were significant predictors of MACE after univariate analyses (OR 3.25, 95% CI 1.78 to 5.96; OR 8.89, 95% CI 3.57 to 22.17 respectively).

Table 3 Patient Characteristics of patients with HEART ≤ 3 versus HEART > 3

Variable	HEART ≤ 3 (n = 172)	HEART > 3 (n = 528)	P value
Age (years)	54 (±12)	67 (±13)	< 0.001
Men (%)	86 (50%)	315 (60%)	0.026
Diabetes Mellitus	9 (5%)	111 (22%)	< 0.001
Body mass index ≥ 30kg/m2	33 (28%)	107 (25%)	0.502
Hypercholesterolemia*	46 (27%)	229 (45%)	< 0.001
Hypertension^	62 (37%)	310 (60%)	< 0.001
Positive family history of CAD	77 (46%)	247 (48%)	0.588
Current smoker	44 (26%)	112 (22%)	0.264
Previous AMI	13 (8%)	137 (26%)	< 0.001
Previous PCI	13 (8%)	162 (31%)	< 0.001
Previous CABG	2 (1%)	64 (12%)	< 0.001
Previous TIA/Stroke	2 (1%)	41 (8%)	0.002
Previous Peripheral artery disease	2 (1%)	29 (6%)	0.017

Values are n (%) or mean ± SD.

CAD = coronary artery disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack.

* Hypercholesterolemia refers to patients receiving lipid-lowering therapy ; ^Hypertension refers to patients receiving blood pressure medication

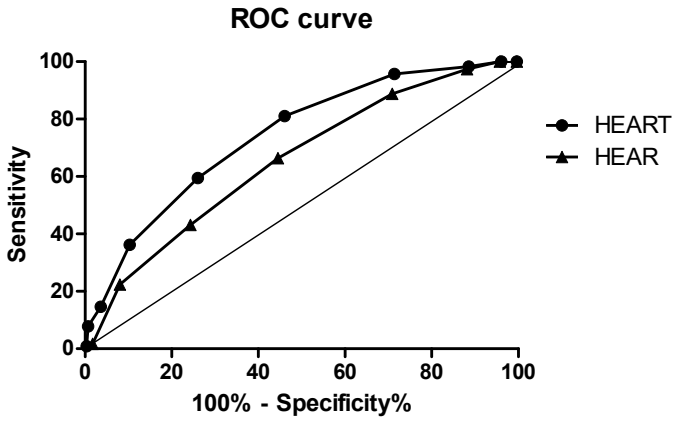

Figure 2 ROC curves of pre-hospital HEAR (AUC 0.65, CI 0.60 to 0.71) versus pre-hospital HEART (AUC 0.74 CI 0.69 to 0.79, p < 0.001) in 700 patients with suspected NSTE-ACS.

Table 4 Patient Characteristics of patients with versus without MACE within 45 days

Variable	MACE (n = 116)	No MACE (n = 584)	P value
Mean age (SD), y	68.05 (±13)	62.67 (±14)	<0.001
Male, n (%)	88 (76%)	313 (54%)	<0.001
HEART ≤ 3	5 (4%)	167 (29%)	<0.001
HEART > 3	111 (96%)	417 (71%)	
HEAR ≤ 3	13 (11%)	170 (29%)	< 0.001
HEAR > 3	103 (89%)	440 (75%)	
Increased Troponin, n (%)	43 (37%)	26 (5%)	< 0.001
Diabetes Mellitus	26 (22%)	87 (15%)	0.044
Body mass index ≥ 30kg/m2	27 (26%)	113 (25%)	0.826
Hypercholesterolemia*	61 (54%)	214 (38%)	0.002
Hypertension^	66 (58%)	306 (54%)	0.421
Positive family history of CAD	47 (41%)	277 (49%)	0.133
Current smoker	30 (27%)	126 (22%)	0.332
Previous AMI	34 (29%)	116 (20%)	0.024
Previous PCI	42 (36%)	133 (23%)	0.002
Previous CABG	14 (12%)	52 (9%)	0.287
Previous TIA/Stroke	11 (10%)	32 (6%)	0.095
Previous Peripheral artery disease	11 (10%)	20 (3%)	0.004

Values are n (%) or mean ± SD.

CAD = coronary artery disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack.

* Hypercholesterolemia refers to patients receiving lipid-lowering therapy ; ^Hypertension refers to patients receiving blood pressure medication

In 73 patients with MACE, the POC troponin test was negative. Median time between onset of complaints and POC troponin assessment in those patients was 85 minutes (IQR 23 to 210). In the 43 patients with MACE and a positive troponin test, median duration of complaints was 240 minutes (IQR 60 to 875, p = 0.001). MACE after 30 days of follow up instead of 45 days follow up was 2.9% in the low-risk HEART group, compared with 20.3% in the intermediate-high HEART risk group (p <0.001). In the low-risk HEAR group, 13 patients (7%) experienced MACE versus 99 (19%) in the intermediate-high risk group.

DISCUSSION

We demonstrated that in suspected NSTE-ACS, the pre-hospital troponin component within the HEART score has important value in predicting MACE within 45 days. The HEART score was designed to incorporate a systematic and integrated approach of patients with suspected non-STEMI.[22] Famous Triage is the first study in which the complete HEART score is investigated in a pre-hospital setting.[2,3,23] The first phase of this study was performed with retrospective HEART assessment and hs-TnT.[2] The current, second phase, was performed with a complete pre-hospital HEART score, including POC TnT assessment.

Previous studies showed that an elevated pre-hospital POC TnT is highly predictive of mortality in patients with a suspected acute myocardial infarction.[16,24] In one study, pre-hospital POC TnT measurement detected 39% of all patients with acute myocardial infarction with an AUC of 0.67.[16] Another study showed an AUC of 0.68[15] for POC TnT diagnosing NSTEMI. It seems that pre-hospital troponin is particularly useful in identifying patients at high risk, but is less suitable for identification of patients at low risk.

Compared with 2 HEART validation studies in which the AUC curves were 0.83[12,13], AUC curves of the pre-hospital HEAR and HEART in our study were lower. A shorter time interval between symptom onset and troponin assessment in the pre-hospital setting is most likely an important contributor to a smaller amount of true high HEART scores. This is supported by a study on single POC TnT assessment which showed that diagnostic accuracy increased when symptom duration was >120minutes.[16] Another explanation can be the slightly higher percentage of patients with MACE in the low-risk group (2.9%) in our study which makes the amount of false negative HEART scores in this study slightly larger. In retrospect, of 5 patients in the low-risk group with MACE, 3 patients were misclassified due to incorrectly scored risk factors by paramedics. The 2 other patients were included early after start of complaints and troponin would have been elevated if a second POC troponin measurement was performed. Lastly, there might be an explanation in a different adjudication of MACE. In the above-mentioned validation studies, non-STEMI and STEMI were considered as MACE, whereas in our study also unstable angina was considered MACE.

Our study had several strengths. Patients in the area of 2 large hospitals, covering rural and more densely populated urban areas of the Netherlands, were included which makes the results well generalizable. The study simulates hospital HEART score implementation as closely as possible without consequential extra burden to paramedics

and patients. A precondition is that paramedics are trained to operate autonomously. In the Netherlands, ambulance paramedics have bachelor degrees in nursing with at least 2 subsequent specializations in critical care nursing. Paramedics in our study were familiar with the HEART score since 2012 and they were additionally trained in assessing the HEART score including troponin assessment before start of this phase of the Famous Triage project. Lastly, we had a complete follow up in almost all patients (99.6%).

This study also has limitations. A complete HEART score was absent in 120 patients (14.6%), mostly due to a missing POC troponin result (87 patients, 73% of missing HEART scores). The main causes of the absence of troponin measurement were device errors of the cobas h 232 POC system and unavailability of testing strips. Hence, the existence of a selection bias cannot be fully excluded. Newly developed POC systems might be more user-friendly and may have less error. The sample size of our study was too small to perform adequate analyses of subgroups. Lastly, although the HEART score is partly validated with 4th generation troponin assessments,[12,13] a hs-TnT POC test may have resulted in better predictive value of HEART.

In the future, pre-hospital instead of in-hospital risk assessment in suspected NSTE-ACS might be applicable by the pre-hospital HEART score. However, there are a few matters to solve before pre-hospital HEART score implementation with subsequent treatment and/or transfer consequences is feasible. The first considers the time interval needed for a reliable troponin measurement. A second troponin measurement, or a second HEART score after > 120 minutes will be more reliable in excluding MACE. This is also in line with the current NSTE-ACS guidelines in which a second troponin assessment is recommended when symptoms started within 6 hours of measurement.[1] The second matter is that the HEART score only predicts MACE within 45 days. Whether a HEART score should be performed in the first place remains to the discretion of the paramedic. Also importantly, paramedics need to evaluate the indication for hospital examination in case of suspicion of a potentially dangerous alternative cause of symptoms. Lastly, a point of concern may be time delay, by ambulance paramedics in collecting blood samples. However, Stengaard *et. al.*, 2013[16] have established that paramedics spent 2 minutes extra on scene when POC troponin is assessed.

A potential future implication is the development of a POC hs-cTnT test. The current hs-cTnT assays which are used in hospital have sensitivities of approximately 90% and several novel strategies for the early rule-out or early rule-in of myocardial infarction already have been invented.[25–28] However, full clinical assessment of patients with suspected non-STEMI remains the gold standard, both for the hospital and pre-hospital setting.[29] Introduction of POC hs-cTnT devices will likely increase the sensitivity of

diagnosing NSTE-ACS, but at the cost of a reduced positive predictive value.[30] Lastly, the current European Society of Cardiology NSTE-ACS guidelines emphasize a more aggressive strategy in high-risk patients with non-STEMI. Future studies should assess whether pre-hospital risk stratification can identify patients with the highest benefit of early angiography and subsequent revascularization.

CONCLUSION

In suspected NSTE-ACS, POC troponin assessment within a pre-hospital HEART score has substantial added value in risk stratifying patients at low- and intermediate-high risk for MACE.

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5

Accuracy of pre-hospital HEART score risk classification using point of care versus high sensitive troponin in suspected NSTE-ACS

Dominique N. van Dongen*, Marion J. Fokkert*, Rudolf T. Tolsma, Aize van der Sluis, Robbert J. Slingerland, Erik A. Badings, Arnoud W.J. van 't Hof, Jan Paul Ottervanger

* equal contribution

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ABSTRACT

Introduction Pre-hospital risk classification by the HEART score is performed with point of care troponin assessment. However, point of care troponin is less sensitive than high sensitive troponin measurement, which is used in the hospital setting. In this study, we compared pre-hospital HEART score risk classification using point of care troponin versus high sensitive troponin.

Methods In 689 consecutive patients with suspected NSTE-ACS, point of care troponin and laboratory high-sensitive troponin were measured in pre-hospital derived blood. For every patient the HEART score with both point of care troponin (HEART-POC) and high sensitive troponin (HEART-hsTnT) was determined. Endpoint was MACE within 45 days.

Results Mean age was 64 (SD±14), 163 (24%) patients were considered low-risk by HEART-hsTnT and 170 (25%) by HEART-POC. MACE was observed in 17%. Although high sensitive versus POC troponin scoring was different in 130 (19%) of patients, in 678 (98%) patients risk classification in low versus intermediate-high risk was similar. The predictive values of HEART-POC versus HEART-HsTnT was similar (AUC 0.75 versus 0.76, p = 0.241).

Conclusion Although high sensitive versus POC troponin scoring was dissimilar in one fifth of patients, this resulted in different patient risk classification in only 2 percent of patients. Therefore, POC troponin measurement suffices for pre-hospital risk stratification of suspected NSTE-ACS.

INTRODUCTION

Early rule out strategies in patients with suspected NSTE-ACS are essential for fast discharge of low-risk patients and efficient use of healthcare resources. Pre-hospital risk assessment in suspected NSTE-ACS using the HEART score has been compared to hospital acquired HEART score assessment and appears to be comparable.[1] However, a pre-hospital HEART score contains point of care troponin (POC) which has lower accuracy compared to laboratory high-sensitivity troponin measurement (hsTnT).[2] This may result in dissimilar risk stratification, with possibly different prognostic relevance. In this study, we compared risk stratification by a pre-hospital HEART score including POC troponin (HEART-POC) with pre-hospital risk stratification including a high sensitive troponin (HEART-hsTnT).

METHODS

Study design and population This prospective observational cohort study, the second phase of the Famous Triage project[3,4], was performed between January 2016 and July 2017. Patients from Isala and Deventer Hospital were included which are tertiary and secondary care hospitals in the Netherlands. The study involved 33 emergency medical services vehicles from 2 regional ambulance services (*Ambulance IJsselland and Witte Kruis ambulancezorg*) staffed by approximately 110 paramedics. The original aim of the second phase of the Famous Triage project was to determine the accuracy of risk stratification by paramedics in patients with suspected NSTE-ACS.[5] The aim of the current study was to compare risk stratification by a pre-hospital HEART score including POC troponin (HEART-POC) with pre-hospital risk stratification including a high sensitive troponin (HEART-hsTnT). The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

The inclusion criteria were out-of-hospital patients with age ≥ 18 years, visited by an ambulance with a pre-hospital suspicion of NSTE-ACS at first medical contact. The exclusion criteria were pregnancy, comatose state, cognitive impairment, shock, cardiac asthma, sustained ventricular tachyarrhythmia, end stage renal disease, an obvious non-cardiac cause for chest complaints or a strong suspicion of aortic dissection or pulmonary embolism. The study was registered in the Dutch Trial Register [http://www.trialregister.nl]: trial number 4205.

Pre-hospital assessment Prior to the start of this study, all paramedics were trained in determining the HEART score including point-of care (POC) troponin measurement. The HEART score is shown in Figure 1. Preceding inclusion, all patients underwent routine assessment including a brief history, monitoring of vital signs (blood pressure, heart rate, pulse oximetry), 12-lead electrocardiogram and intravenous access, according to local emergency medicine service protocols. Pre-hospital HEART score assessment by paramedics was described previously[5]. A pre-hospital cardiac troponin T assay was performed on site using the Roche CARDIAC POC troponin T test on the cobas h 232 POC system with a detection range of 40 – 2000 ng/L. Blood was derived after insertion of a venous line. POC test results were available in 8 – 12 minutes. The HEART score was originally validated with mostly high sensitive troponin assays[6] in which the upper reference limit is 14 ng/L. Originally 1 point was given when troponin was elevated between 1-3 times the upper reference limit and 2 points when troponin was elevated ≥ 3 times the upper reference limit. Because 3 times 14 is 42 ng/L, it was impossible to adjudicate 1 point for troponin with the used POC troponin assessment. Therefore a troponin value below 40ng/L scored 0 points and a troponin value exceeding 40 ng/L scored 2 points.

Besides POC testing in the ambulance, the same blood that was derived for the POC test was collected to assess high-sensitive cardiac troponin T (hs-cTnT) at the clinical chemistry laboratory using the hs-cTnT Modular and Cobas 8000 system of Roche Diagnostics, Manheim, Germany, with a limit of detection of 3 ng/L and inaccuracy corresponding to a 10% coefficient of variation at the 99th percentile upper reference limit (URL) of the reference population. A hs-cTnT value exceeding the 99th percentile URL (14 ng/L) was considered elevated. Hospital troponin was scored 0 (hs-cTnT ≤ 14ng/L), 1 (hs-cTnT 1-3 times URL) or 2 (hs-cTnT ≥ 3 times URL). Low-risk was defined as a HEART score ≤ 3.

Diagnostic adjudication Adjudication of the final diagnosis was performed by applying current guidelines and the third universal definition of myocardial infarction.[7–9] Cardiac ischemia was defined as ST-segment elevation myocardial infarction (STEMI), which was determined by ECG judgement, non-ST-segment elevation myocardial infarction (non-STEMI) and unstable angina. Non-STEMI diagnosis was made when the in-hospital cardiac high sensitive troponin value was above the 99th percentile upper reference limit (14 ng/mL) with a significant delta after serial sampling with 3 hours interval as well as ECG judgement and a clinical setting consistent with myocardial ischemia. Unstable angina was diagnosed as a clinical setting consistent with myocardial ischemia and normal cardiac high sensitive troponin or above the 99th percentile upper reference limit without a significant delta. All other patients were diagnosed with stable angina, non-

cardiac chest pain or cardiac but non-coronary disease (e.g., tachyarrhythmias, heart failure). A percutaneous coronary intervention (PCI) was defined as a percutaneous strategy of therapeutic intracoronary balloon dilatation and/or stent placement. A CABG was defined as a surgical procedure of coronary artery grafting as to bypass a coronary stenosis.

Figure 1 HEART score

HEART score			
History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥ 65 years	2	
	> 45 and <65 years	1	
	≤ 45 years	0	
Risk factors*	≥ 3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin°	≥ 3x normal limit	2	
	1-2 x normal limit	1	
	Normal limit or lower	0	
		Total	

* Risk factors: Hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, BMI > 30kg/m²

° POC troponin below 40ng/L was scored 0, values exceeding 40 ng/L scored 2 points. Hospital troponin was scored according this figure.

ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; PM = pacemaker.

The outcome was the occurrence of MACE within 45 days after inclusion. MACE was defined as acute coronary syndrome comprising STEMI, NSTEMI or unstable angina; death by all cause, PCI or CABG. To identify MACE, medical record studies were performed. When there was no in-hospital follow up after 45 days, patients were contacted by telephone or via the patient's general practitioner. Information regarding death was obtained from the national registry on mortality.

Statistical analysis Statistical analysis was performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA) and R (R Core Team, 2018). Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR). Variables were tested for normality of distribution. For the comparison of normally distributed variables a *t* test was used to compare means, for non-normally distributed variables a non-parametric variant (Mann - Whitney *U* test) was used. Categorical variables were reported by frequencies and percentages and were compared with chi-square test. To evaluate the predictive value of the pre-hospital HEART and hospital HEART scores for MACE within 45 days, receiver operator characteristics (ROC) analyses were performed. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

From January 2016 to July 2017 a total of 823 patients were deemed eligible by paramedics. A complete pre-hospital HEART score was not available in 120 patients (14.6%) due to missing troponin results (87 patients) or incomplete registration of other HEART score components (41 patients). Three patients were lost to follow up. Of 700 patients (85.1%) with a complete pre-hospital HEART score and follow up, 689 patients had blood specimens available for high sensitive troponin measurement.

Table 1 Demographics and Presenting Features of low versus intermediate-high risk patients with suspected NSTE-ACS

Variable	HEART HsTnT ≤3 N = 163	HEART HsTnT >3 N = 526
Male	82 (50%)	312 (59%)
Age, mean (SD), y	54 (12)	67 (13)
Smoking	43 (26%)	109 (21%)
Hypertension	57 (35%)	308 (59%)
Diabetes	8 (5%)	110 (22%)
Dyslipidemia	42 (26%)	229 (44%)
Coronary artery disease	13 (8%)	210 (40%)
Peripheral vascular disease	2 (1%)	27 (5%)
Previous PCI	12 (7%)	159 (30%)
Previous CABG	1 (1%)	62 (12%)
Previous TIA or stroke	2 (1%)	40 (8%)
Time from symptom onset, median (IQR), min	142 (60 – 365)	150 (65 – 460)
Complaints > 6 h	44 (27%)	162 (31%)

Patient characteristics are shown in table 1. Mean age of the total group was 64 years (SD ±14), 57% was male. Prevalence of smoking was 34%, hypertension 54%, and a history of prior PCI 25%. The intermediate to high-risk patients were older, more often male, had a significantly higher prevalence of cardiovascular risk factors and significantly more often prior atherosclerotic diseases. Patients with low risk according HEART-POC had a significantly shorter complaint duration than patients at intermediate-high risk (120 versus 152 minutes, p = 0.041). A contingency table of POC troponin versus high sensitive troponin shows a discrepancy in scoring of the T component of the HEART score in 128 (19%) patients with 111 patients scoring higher and 18 patients scoring lower with hs-TnT compared to POC troponin (table 2).

170 Patients were considered as low risk (HEART score ≤3) according HEART-POC versus 163 according HEART-hsTnT (Table 3). 678 (98%) Patients had similar risk classification (kappa 0.956). The cumulative incidence of MACEs within 45 days in the study group was 17%. 38 Patients with MACE had both non-elevated POC and hs-TnT. 33 Patients with MACE had normal POC values and elevated hs-TnT and in 43 patients with MACE, both troponin tests were elevated. In both low-risk groups, 5 patients (2.9%) experienced MACE with no deaths. From 11 patients with dissimilar risk classification, 2 patients experienced MACE; one of them was classified as low risk by the HEART-POC and one as low risk by the HEART- HSTnT score (Table 4). Odds ratio for MACE of

p-value	HEART POC ≤3 N = 170	HEART POC >3 N = 519	p-value
0.042	85 (50%)	309 (60%)	0.029
<0.001	53 (12)	67 (13)	<0.001
0.146	43 (25%)	109 (21%)	0.28
<0.001	61 (36%)	304 (59%)	<0.001
<0.001	9 (5%)	109 (21%)	<0.001
<0.001	44 (26%)	226 (44%)	<0.001
<0.001	15 (9%)	208 (40%)	<0.001
0.03	2 (1.2%)	27 (5%)	0.023
<0.001	13 (8%)	158 (30%)	<0.001
<0.001	2 (1%)	61 (12%)	<0.001
0.003	2 (1%)	40 (8%)	0.002
0.114	120 (60 – 375)	152 (70 – 455)	0.041
0.354	45 (27%)	161 (31%)	0.26

elevated hsTnT was 10 (95% CI 6 – 15). Elevated POC troponin was the best predictor of MACE (OR 16, 95% CI 9 – 28). HEART-POC or HEART-hsTnT > 3 had predictive value of OR 8.77 (3.52 – 21.0) and 8.26 (3.31 – 20.62), respectively.

Table 2 Pre-hospital troponin component score of the HEART score with POC troponin versus high sensitive troponin in 689 patients with suspected NSTE-ACS

		HsTnT			Total
		0	**1**	**2**	
POC	**0**	515	110	1	626
	2	0	18	45	63
Total		515	128	46	689

Table 3 Pre-hospital HEART POC versus HEART hs-TnT in 689 patients with suspected NSTE-ACS

		HEART HsTnT		Total
		≤ 3	**> 3**	
HEART POC	**≤ 3**	161	9	170
	> 3	2	517	519
Total		163	526	689

Table 4 Pre-hospital HEART POC versus HEART hs-TnT in 114 patients with MACE

		HEART HsTnT		Total
		≤ 3	**> 3**	
HEART POC	**≤ 3**	4	1	5
	> 3	1	108	109
Total		5	109	114

ROC curves including area under the curve (AUC) for the prediction of MACE by HEART-POC (0.75, 95% CI 0.71 – 0.80) versus HEART-hsTnT (0.76, 95% CI 0.71 – 0.80) are depicted in Figure 2. Predictive value for MACE showed no significant difference (p = 0.241).

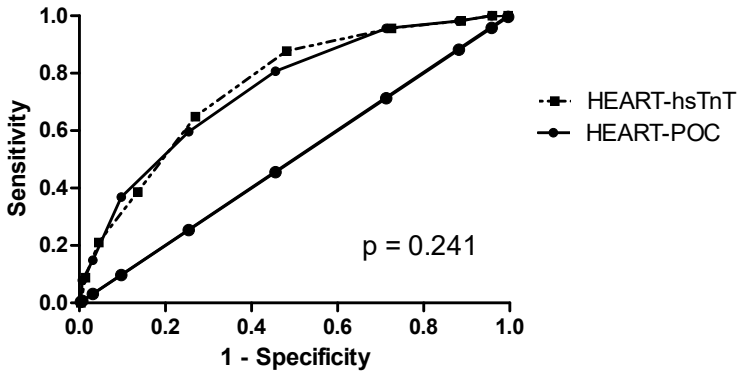

Figure 2 ROC curves for pre-hospital HEART-POC versus HEART-hsTnT for prediction of MACE within 45 days MACE. ROC curves of HEART-POC (0.745 95% CI 0.698 to 0.793) versus pre-hospital HEART (AUC 0.756 95% CI 0.71 to 0.801, p = 0.241) in 689 patients with suspected NSTE-ACS.

DISCUSSION

This prospective observational study demonstrated that in suspected NSTE-ACS, risk stratification according the HEART score using point of care versus high sensitive troponin is similar. Famous Triage is the first study in which pre-hospital risk stratification, including troponin assessment, is completely carried out by paramedics using the HEART score.[3,4,10]

Our findings are compatible with a study of Mahler *et al.*,[11] which showed that the hospital HEART score using cardiac troponin I versus high sensitive troponin I had similar performance (both achieved 100% sensitivity and negative predictive value for MACE). Another hospital study showed that an improved POC troponin I is comparable to a high sensitive troponin when used in a diagnostic protocol[12]. This is also comparable to our finding that HEART-POC and HEART-hsTnT result in similar risk stratification. However, both abovementioned studies used POC troponin I unlike our study in which POC troponin T is used, which makes direct comparison not possible. Previous studies showed that an elevated pre-hospital POC troponin is highly predictive of mortality in patients with a suspected acute myocardial infarction.[13,14] In one study, pre-hospital POC TnT measurement detected 39% of all patients with acute myocardial infarction with an AUC of 0.67.[14] Another study showed an AUC of 0.68[15] for POC troponin diagnosing NSTEMI. Also, it was shown that high sensitive cardiac troponin measurement without clinical risk assessment is insufficiently sensitive for rule out of myocardial infarction.[11,16,17] This is comparable to our results which show that 38 patients with MACE

within 45 days had normal hs-TnT whereas only 5 patients remained low-risk when HEART score risk stratification was applied. The abovementioned findings suggest that solitary pre-hospital troponin is particularly useful in identifying patients at high risk for acute NSTE-ACS, but additional clinical risk stratification is necessary to optimize the safety and effectiveness of rule-out strategies for MACE within a few weeks. This suggestion is confirmed by a recent study which showed that the addition of a HEART score to the European Society of Cardiology pathway improved the negative predictive value from 97.9% to 99.7%.[18]

Another point to mention is the time interval between start of complaints and troponin assessment. Our results show that the median time interval was 142 minutes in the low-risk HEART-hsTnT group and 120 minutes in the HEART-POC group. Current guidelines recommend a second troponin assessment when complaints started within 6h of presentation.[7] This is supported by a study on single POC troponin assessment without HEART score assessment which showed that diagnostic accuracy increased when symptom duration was > 120 min.[14] Further research is needed to investigate whether a second troponin measurement should be performed to improve safety or that pre-hospital risk stratification is only possible in patients with a complaint onset of more than 6h ago.

Strengths Our study has several strengths. First, this is the first study in which the HEART score is prospectively performed in the pre-hospital setting with POC and high sensitive troponin measurement from the same blood withdrawal. We had follow up of almost all patients. This study has significant value when the aim is to relocate risk assessment from the hospital to a pre-hospital setting in the future.

Limitations Our study also had some noteworthy limitations. A complete pre-hospital HEART score was absent in 120 patients (14.6%), mostly due to a missing POC troponin measurement (72.5%). Hereby, a potential selection bias cannot be fully excluded. Absence of troponin measurements was mainly attributed to device errors of the cobas h 232 POC system. Another cause was the inability to obtain blood from the peripheral venous canula. Possibly, newly developed POC systems are more user-friendly and may have fewer errors. Also integration of venous blood sampling in local EMS protocols might better facilitate the ability to perform POC troponin assessment. The sample size of our study was too small to perform analyses of subgroups. Possibly, pre-hospital HEART score risk stratification is not suitable in patients with short duration of complaints. This should be further investigated. Lastly, we only investigated POC troponin T and high sensitive troponin T. Clinical significance of the results is therefore limited to these specific assays and cannot be generalized to other cardiac troponin assays.

Future implications of our study There are several studies that investigated hospital HEART score implementation for prediction of MACE[6,19,20], its positive effect on healthcare utilization, costs and time efficiency on the emergency department[21–23] and decreased hospitalizations or faster discharge from the emergency department.[24] However, when HEART-POC is similar to HEART-hsTnT it might even not be necessary to transfer very low-risk patients with suspected NSTE-ACS to the hospital.[4,5] Subsequently, hospital admissions can be further decreased, unnecessary transport of patients and possible hospital overcrowding can be avoided and healthcare utilization can become more efficient.

CONCLUSION

Risk classification according the HEART score with point of care versus high sensitive troponin shows similar risk classification and prediction of MACE. Possibly, pre-hospital risk stratification can replace hospital risk stratification in the future.

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Pre-hospital versus hospital acquired HEART score for risk classification of suspected NSTE-ACS

Dominique N. van Dongen, Erik A. Badings MD, Marion J. Fokkert, Rudolf T. Tolsma, Aize van der Sluis, Robbert J. Slingerland, Arnoud W.J. van 't Hof, Jan Paul Ottervanger

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ABSTRACT

Introduction Although increasing evidence shows that in patients with suspected non-ST-elevation acute coronary Syndrome (NSTE-ACS) both hospital and pre-hospital acquired HEART (History, ECG, Age, Risk factors, Troponin) scores have strong predictive value, pre-hospital and hospital acquired HEART scores have never been compared directly.

Methods In 699 patients with suspected NSTE-ACS, the HEART score was independently prospectively assessed in the pre-hospital setting by ambulance paramedics and in the hospital by physicians. The hospital HEART score was considered the gold standard. Low-risk (HEART score ≤ 3) was considered a negative test. Endpoint was occurrence of major adverse events within 45 days.

Results A total of 699 patients were included in the analyses. In 516 (74%) patients pre-hospital and hospital risk classification was similar, in 50 (7%) pre-hospital risk classification was false negative (45 days mortality 0%) and in 133 (19%) false positive (45 days mortality 1.5%). False negative risk classifications were caused by differences in history (100%), risk factor assessment (66%), and troponin (18%), and was more common in older patients. Occurrence of major adverse events was comparable in pre-hospital and hospital low-risk patients (2.9 versus 2.7%, $p = 0.9$). Incidence of major adverse events was 0% in the true negative group, 26% in the true positive group, 10% in the false negative group and 5% in the false positive group. Predictive value of both pre-hospital and hospital acquired HEART scores was high, although the 'area under the curve' of hospital acquired HEART score was higher (0.84 vs 0.74, $p < 0.001$).

Conclusion In approximately 25% of patients hospital and pre-hospital HEART score risk classification disagree, mainly by risk overestimation in the pre-hospital group. Since disagreement is primarily caused by different scoring of history and risk factors, additional training may improve pre-hospital scoring.

INTRODUCTION

Early risk assessment in patients with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS) facilitates early treatment decisions.[1] The HEART (History, ECG, Age, Risk factors, Troponin) score (figure 1) is a risk score from 0 to 10 points, combining clinical parameters, electrocardiogram (ECG) findings and troponin values to stratify patients with suspected NSTE-ACS to low, intermediate or high risk for major adverse cardiac events (MACE)[2] A number of studies have validated the HEART score in the hospital setting.[2–4] However, troponin measurement is nowadays possible in the ambulance and therefore, the HEART score can be completely obtained in the pre-hospital setting.[5,6] So far, several studies showed that pre-hospital risk classification by paramedics using the HEART score is feasible and shows high sensitivity and negative predictive value in terms of MACE (MACE: revascularization, acute coronary syndrome, death) within 45 days.[7,8] However, pre-hospital and hospital acquired HEART scores have never been compared directly. The aim of this study was to compare pre-hospital with hospital performed risk classification by using the HEART score in patients with suspected NSTE-ACS and to compare the predictive value of both methods in terms of MACE after 45 days follow up.

Figure 1 HEART score

HEART score			
History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥ 65 years	2	
	> 45 and <65 years	1	
	≤ 45 years	0	
Risk factors*	≥ 3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin°	≥ 3x normal limit	2	
	1-2 x normal limit	1	
	Normal limit or lower	0	
		Total	

* Risk factors: Hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, BMI > 30kg/m^2

°Point-of-care troponin below 40 ng/L was scored 0, values exceeding 40 ng/L scored two points. Hospital troponin was scored according to this figure.

ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; PM = pacemaker.

METHODS

Study design and population Famous Triage was the first study in which the complete HEART score was investigated in a pre-hospital setting.[2,3,9] The first observational phase of this study was performed with retrospective HEART assessment and high sensitivity troponin T.[3] The second observational phase was performed with a complete pre-hospital HEART score, including point of care troponin T assessment.[8] This prospective observational cohort study, was performed between January 2016 and July 2017. Patients were included from Isala hospital Zwolle and Deventer Hospital, which are tertiary and secondary care hospitals in the Netherlands. The study involved 33 emergency medical services vehicles from two regional ambulance services (Ambulance IJsselland and Witte Kruis ambulancezorg) staffed by approximately 110 paramedics. In The Netherlands, paramedics are trained to operate autonomously. They have bachelor degrees in nursing with at least 2 subsequent specializations in critical care nursing (i.e. intensive care, cardiac care, nurse anaesthetist). The original aim of the second phase of the Famous Triage project was to determine the accuracy of risk stratification by paramedics in patients with suspected NSTE-ACS.[8] The aim of the current study was to compare pre-hospital HEART score risk classification performed by paramedics with in-hospital HEART score risk classification, performed by physicians. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

The inclusion criteria were out-of-hospital patients with age ≥ 18 years, visited by an ambulance with a pre-hospital suspicion of NSTE-ACS at first medical contact. The exclusion criteria were pregnancy, comatose state, cognitive impairment, shock, cardiac asthma (symptoms of heart failure), sustained ventricular tachyarrhythmia, end stage renal disease, an obvious non-cardiac cause for chest complaints or a strong suspicion of aortic dissection or pulmonary embolism. The study was registered in the Dutch Trial Register (http://www.trialregister.nl): trial number 4205.

Routine clinical assessment Prior to the start of this study, all paramedics were trained in determining the HEART score including point of care (POC) troponin measurement. Preceding inclusion, all patients underwent routine assessment including a brief history, monitoring of vital signs (blood pressure, heart rate, pulse oximetry), 12-lead ECG and intravenous access, according to local emergency medicine service protocols. For pre-hospital HEART score assessment, ECG analyses were performed by the ambulance paramedics. ECG interpretation was not performed by use of a computer program. In case of uncertainty the paramedics were able to contact a cardiologist and sent the ECG digitally. If the ECG was 'normal' according to Minnesota criteria, zero points were given.

In case of repolarization abnormalities without significant ST-segment depression, one point was given. One point was also granted in case of a bundle branch block. For significant ST-segment depressions in the absence of a bundle branch block two points were given. Risk factors and medication use necessary for pre-hospital HEART assessment were collected by using standard questionnaires. A pre-hospital cardiac troponin T assay was performed on site using the Roche CARDIAC POC troponin T test on the cobas h 232 POC system with a limit of detection of 40 – 2000 ng/L. Blood was derived after insertion of a venous line. POC test results were available in 8 – 12 minutes. Measurements during driving were avoided. The HEART score was originally validated with mostly high sensitive troponin assays[3] in which the upper reference limit is 0.014 ng/mL. Originally 1 point was given when troponin was elevated between one and three times the upper reference limit and two points when troponin was elevated ≥ 3 times the upper reference limit. Because 3 times 0.014 is 0.042 ng/mL, it was impossible to adjudicate one point for troponin with the used POC troponin assessment. Therefore a troponin value below 40ng/L was scored 0 points and a troponin value exceeding 40 ng/L scored two points.

In the hospital, physicians were not informed about the outcome of the pre-hospital assessed HEART score. High-sensitivity cardiac troponin T (hs-cTnT) was assessed at the clinical chemistry laboratory using the hs-cTnT Modular and Cobas 8000 system of Roche Diagnostics, Manheim, Germany, with a limit of detection of 3 ng/L and inaccuracy corresponding to a 10% coefficient of variation at the 99th percentile upper reference limit (URL) of the reference population. The troponin results of the first blood withdrawal after arrival at the emergency department were used by the physician for HEART score assessment. These troponin results were available after 45-60 min. A hs-cTnT value exceeding the 99th percentile URL (14 ng/L) was considered elevated. Hospital troponin was scored 0 (hs-cTnT ≤ 14ng/L), 1 (hs-cTnT 1-3 times URL) or 2 (hs-cTnT ≥ 3 times URL). Both pre-hospital and hospital HEART scores were registered in separate digital patient electronic files. Low-risk was defined as a HEART score ≤ 3.

Diagnostic adjudication Adjudication of the final diagnosis was performed by applying current guidelines and the third universal definition of myocardial infarction.[1,9,10] Cardiac ischemia was defined as ST-segment elevation myocardial infarction (STEMI), which was determined by ECG judgement, non-ST-segment elevation myocardial infarction (nSTEMI) and unstable angina. NSTEMI diagnosis was made when the in-hospital cardiac high sensitive troponin value was above the 99th percentile upper reference limit (14 ng/mL) with a significant delta after serial sampling with 3 hours interval as well as ECG judgement and a clinical setting consistent with myocardial ischemia. Unstable angina was diagnosed as a clinical setting consistent with myocardial ischemia and

normal cardiac high sensitive troponin or above the 99th percentile upper reference limit without a significant delta. All other patients were diagnosed with stable angina, non-cardiac chest pain or cardiac but non-coronary disease (e.g., tachyarrhythmias, heart failure). A percutaneous coronary intervention (PCI) was defined as a percutaneous strategy of therapeutic intracoronary balloon dilatation and/or stent placement. A CABG was defined as a surgical procedure of coronary artery grafting as to bypass a coronary stenosis.

The outcome was the occurrence of MACE within 45 days after inclusion. MACE was defined as ACS comprising STEMI, NSTEMI or unstable angina; death by all cause, PCI or CABG. To identify a MACE, medical record studies were performed. When there was no in-hospital follow up after 45 days, patients were contacted by telephone or via the patient's general practitioner. Information regarding death was obtained from the national registry on mortality.

Statistical analysis Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA) and R (R Core Team, 2018). Continuous variables were expressed as mean ± standard deviation or median with interquartile range. Variables were tested for normality of distribution. For the comparison of normally distributed variables a *t* test was used to compare means, for non-normally distributed variables a non-parametric variant (Mann - Whitney U test) was used. Categorical variables were reported by frequencies and percentages and were compared with chi-square test. Intraclass correlation coefficients were calculated to determine the level of agreement. To evaluate the predictive value of the pre-hospital HEART and hospital HEART scores for MACE within 45 days, receiver operator characteristics (ROC) analyses were performed. A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

From January 2016 to July 2017 a total of 823 patients were deemed eligible by paramedics. A flow chart is provided in Figure 2. A complete pre-hospital HEART score was not available in 120 patients (14.6%) due to missing troponin results (87 patients) or incomplete registration of other HEART score components (41 patients). Three patients were lost to follow up. Of 700 patients (85.1%) with a complete pre-hospital HEART score and follow up, one patient missed hospital HEART score registration. Therefore, 699 patients were included in the analysis.

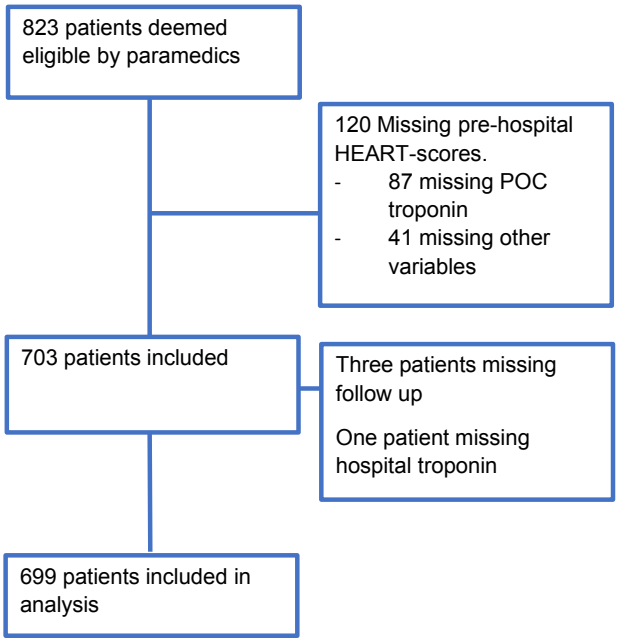

Figure 2 Flow chart of patient inclusion. HEART: History, ECG, Age, Risk factors and initial Troponin; POC: point-of-care

Patient characteristics are shown in table 1. Mean age of the total group was 63.6 years (SD ±13.6), 57% was male. Prevalence of hypercholesterolemia was 41%, hypertension 55% and previous PCI 25%. Correctly scored patients were significantly older, had more often diabetes, and more often previous acute myocardial infarction, PCI or CABG. A contingency table of risk classification by pre-hospital versus hospital risk classification is shown (Table 2, Figure 3). In 516 (74%) patients pre-hospital risk classification was correct according to hospital risk classification. Intraclass correlation coefficient (ICC) for the HEART score as an ordinal variable was 0.784 (95% CI 0.750 – 0.814).

Univariate logistic regression analysis showed that older age odds ratio (OR) 0.97, p <0.001), diabetes mellitus (OR 0.47, p = 0.005), hypertension (OR 0.67, p = 0.023), previous PCI (OR 0.34, p <0.001) and previous CABG (OR 0.26, p = 0.002) were significantly associated with concordance in risk classification. In multivariate logistic regression analysis only previous PCI (OR 0.42, p = 0.019), previous CABG (OR 0.37, p = 0.046) and age (OR 0.98, p = 0.001) were independently related to concordance in risk classification. Duration of complaints had no significant effect on differences in risk classification. In 50 (7%) patients, paramedics classified patients as low-risk whereas physicians classified patients at intermediate-high risk (false-negative). Hypercholesterolemia and

hypertension were significantly associated with false negative risk classification (Table 3). In 133 (19%) patients, risk classification was false positive. Younger age, absence of previous myocardial infarction and no previous revascularization were significantly associated with false positive risk classification (all p < 0.001).

Table 1 Patient Characteristics of patients scored correct versus incorrect by paramedics according the hospital HEART

Variable	All patients N = 699	'Correct' N = 516	Incorrect N = 183	P value*
Age (years, SD)	63.57 (13.63)	65.14 (14.05)	59.18 (11.29)	<0.001
Men (%)	401 (57)	296 (57%)	105 (57%)	0.998
Diabetes Mellitus	120 (17%)	101 (20%)	19 (11%)	0.004
Body mass index ≥ 30kg/m2	140 (25%)	100 (25%)	40 (27%)	0.55
Hypercholesterolemia*	275 (41%)	212 (42%)	63 (35%)	0.102
Hypertension^	372 (55%)	287 (57%)	85 (47%)	0.023
Positive family history of CAD	324 (48%)	231 (46%)	93 (52%)	0.21
Current smoker	156 (23%)	107 (22%)	49 (27%)	0.11
Previous AMI	150 (22%)	128 (25%)	22 (12%)	<0.001
Previous PCI	175 (25%)	152 (30%)	23 (13%)	<0.001
Previous CABG	66 (9%)	60 (12%)	6 (3%)	0.001
Previous TIA/Stroke	43 (6%)	36 (7%)	7 (4%)	0.127
Previous Peripheral artery disease	31 (4%)	27 (5%)	4 (2%)	0.085
Duration of complaints, (minutes, SD)	661 (1827)	701 (1845)	549 (1773)	0.335
Complaints > 3 hours	337 (48%)	246 (48%)	91 (50%)	0.63
Complaints > 6 hours	211 (30%)	157 (30%)	54 (30%)	0.82

Values are n (%) or mean ± standard deviation (SD).

* P value is for comparison between correct versus incorrect subgroups

CAD = coronary artery disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack.

Table 2 Contingency table of hospital versus pre-hospital risk classification

		Hospital acquired HEART score		**Total**
		Low risk	**Intermediate – high risk**	
Pre-hospital acquired HEART	**Low risk**	122 (47,8%)	50 (11,3%)	172 (24,6%)
	Intermediate – high risk	133 (52,2%)	394 (88,7%)	527 (75,4%)
Total		255 (100,0%)	444 (100,0%)	699 (100,0%)

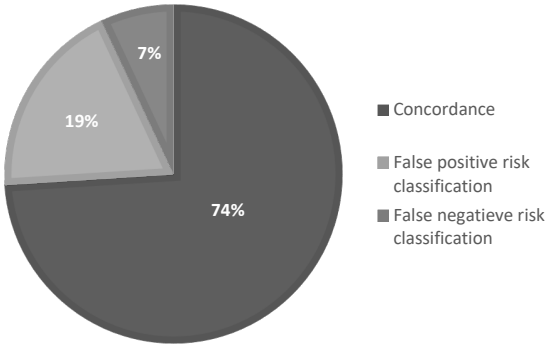

Figure 3 Pre-hospital versus hospital risk classification

Table 3 Patient Characteristics of patients with false negative versus true negative pre-hospital risk classification according to hospital risk classification

Variable	False negative N = 50	True negative N = 122	P value
Age (years)	60.26 (12.14)	51.29 (11.23)	<0.001
Men (%)	29 (58%)	57 (46.7%)	0.18
Diabetes Mellitus	4 (3.3%)	5 (10%)	0.08
Body mass index ≥ 30kg/m2	13 (33%)	20 (25%)	0.34
Hypercholesterolemia*	26 (53%)	29 (17%)	<0.001
Hypertension^	27 (54%)	35 (29%)	0.002
Positive family history of CAD	27 (54%)	50 (42%)	0.17
Current smoker	16 (33%)	28 (24%)	0.22
Previous AMI	6 (12%)	7 (6%)	0.16
Previous PCI	6 (12%)	7 (6%)	0.16
Previous CABG	2 (4%)	0 (0%)	0.026
Previous TIA/Stroke	0 (0%)	2 (2%)	0.36
Previous Peripheral artery disease	1 (2%)	1 (0.8%)	0.51
Duration of complaints, minutes mean (SD)	339 (379)	503 (1233)	0.36
Complaints > 3 hours	26 (52%)	52 (43%)	0.26
Complaints > 6 hours	13 (26%)	34 (28%)	0.85

Values are n (%) or mean ± SD.

CAD = coronary artery disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TIA = transient ischemic attack.

* Hypercholesterolemia refers to patients receiving lipid-lowering therapy ; ^Hypertension refers to patients receiving blood pressure medication

Table 4 Differences in HEART score components in the total, false negative and false positive risk classification groups

		History
Total group N = 699	Same score	285 (41%)
	Pre-hospital lower	124 (18%)
	Pre-hospital higher	291 (42%)
False negative N = 50	Same score	0 (0%)
	Pre-hospital lower	50 (100%)
	Pre-hospital higher	0 (0%)
False positive N = 133	Same score	23 (17%)
	Pre-hospital lower	1 (1%)
	Pre-hospital higher	109 (82%)
ICC for the total group (95% CI)		0.392 (0.294 – 0.476)

HEART: History, ECG, Age, Risk factors and initial Troponin; ECG: Electrocardiogram; ICC: intraclass correlation coefficient; CI: confidence interval

Table 4 shows differences in HEART score components in the total, the false negative and false positive risk classification groups and ICC per HEART variable. False negative risk classification was mainly caused by differences in history (100%) and risk factor scoring (66%). False positive risk classification was also mainly caused by differences in history (82%) another main cause was difference in ECG scoring (59%). Troponin scoring was the same in 549 (79%) of patients. In 18 patients (3%) POC troponin produced a higher score than hospital troponin, in 132 patients (19%) a lower score.

The cumulative incidence of MACEs within 45 days in the study group was 16.6%. In the pre-hospital low-risk patients, 5 patients (2.9%) experienced MACE with no deaths. In the hospital low-risk patients, seven patients (2.7%) experienced MACE with two deaths (p = 0.9 for difference in MACE). Table 5 shows a reclassification table of patients with and without MACE by pre-hospital compared to hospital HEART score risk classification. The 5 'missed' MACE patients by pre-hospital risk classification were all considered intermediate-high risk by hospital risk classification. The seven MACE patients that were considered low-risk according to hospital risk classification were all scored at intermediate-high risk by pre-hospital risk classification. In patients that were considered at low-risk by both pre-hospital and hospital risk classification, no MACE occurred.

ECG	Risk factors	Troponin
390 (56%)	412 (59%)	549 (79%)
71 (10%)	162 (23%)	132 (19%)
239 (34%)	126 (18%)	18 (3%)
38 (76%)	17 (34%)	41 (82%)
7 (14%)	33 (66%)	9 (18%)
5 (10%)	0 (0%)	0 (0%)
53 (40%)	68 (51%)	128 (96%)
1 (1%)	14 (11%)	4 (3%)
79 (59%)	51 (38%)	1 (1%)
0.524 (0.448 – 0.590)	0.618 (0.557 – 0.671)	0.820 (0.792 – 0.845)

ROC curves including area under the curve (AUC) for the prediction of MACE by the pre-hospital versus the hospital HEART score are shown in Figure 4. The AUC for pre-hospital HEART score was 0.74 (95% CI 0.69 to 0.79) and 0.84 (95% CI 0.80 to 0.88) for hospital HEART score ($p < 0.001$).

Table 5 Reclassification table of patients with and without MACE by pre-hospital compared to hospital HEART score risk classification.

MACE		**Hospital HEART**		**Total, MACE and no MACE separate**	**Total**
No MACE		**> 3**	**≤ 3**		
Ambulance HEART	**> 3**	104	7	111	527
		290	126	416	
	≤ 3	5	0	5	172
		45	122	167	
Total, MACE and no MACE separate		109	7	116	
		335	248	583	
Total		444	255		699

Net reclassification index for pre-hospital HEART risk classification = −0.314

HEART: History, ECG, Age, Risk factors and initial Troponin; MACE: major adverse cardiac event.

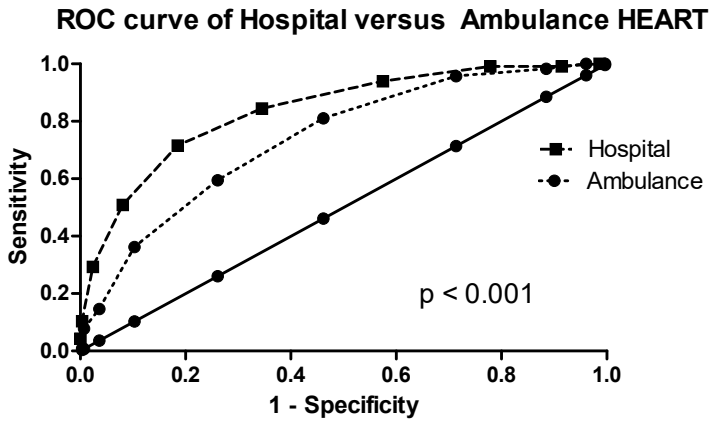

Figure 4 ROC curves of hospital (0.84 95% CI 0.80 to 0.88, p < 0.001) versus pre-hospital HEART (AUC 0.74 95% CI 0.69 to 0.79) in 699 patients with suspected NSTE-ACS.

DISCUSSION

This prospective observational study demonstrated that in suspected NSTE-ACS, risk classification by paramedics using the HEART score is in 74% comparable to risk classification according the validated hospital HEART score. Famous Triage is the first study in which pre-hospital risk classification, including troponin assessment, is completely carried out by paramedics using the HEART score.[7,11,12] Furthermore, this is the first study comparing pre-hospital with hospital risk classification according the HEART score.

There are a few studies comparing HEART scoring between different medical professions. One study analysed discordance between 33 HEART scores that were retrospectively determined by emergency department physicians and cardiologists based on documentation.[13] When categorized into low-risk or high-risk by the HEART Pathway, more than 25% of patients were classified as high risk by the ED physician, but low risk by the cardiologist (false positive risk classification). This is higher than in our study in which the percentage of pre-hospital false positive risk classifications was 19%. In a second study, the HEART score was retrospectively determined by dossier study in 250 patients[14], in 31% of patients there was no inter-observer agreement when the HEART score was digotomised (≤ 3 vs > 3). In our study, there was no inter-observer agreement in 26% of patients. In an external validation study of the HEART score, the kappa coefficients for double entry components and composite HEART scores were calculated.[15] The HEART

scores were retrospectively determined based on dossier study. During the study, senior observers reviewed each abstractor's first 10 completed charts and provided remedial training for any incorrect data entries. In that study, kappa coefficients per HEART item were: history 0.662, ECG 0.917, age 0.981, risk factors 0.906, and troponin 1. Kappa coefficient for the composite HEART score was 0.726. Percentages of agreement or misclassification were not reported. When comparing the abovementioned studies to our study, there are a several substantial differences to mention. First, all studies were retrospective dossier studies in which the HEART scores were based on documented clinical assessment of another person than the HEART score reviewer. Second, all studies were performed in the hospital based on the same patient dossier. This means that the same source of history documentation, ECG performance, risk factor documentation and troponin assessment was used by the HEART score assessors. Those two points are very different from our study in which all HEART components were prospectively and independently assessed by paramedics and physicians in different settings and recorded in different patient dossiers. The findings in the abovementioned studies are also dissimilar. While the first study reports very poor inter-observer agreement[13], the two others show much higher inter-observer agreement.[14,15]

A fourth study shows more similarities to our study.[16] Primary outcome of this study was the interoperator reliability of the HEART score as performed in the ED by different grades of doctor or nurse. In this study patients were prospectively interviewed by clinicians from four different categories and an ICC was calculated. The ICC for the overall HEART Score was 0.91. When the HEART Score was dichotomized (≤ 3 vs > 3), the ICC was 0.84 (95% CI 0.79 to 0.89). The ICC for troponin and age were '1', for 'history' 0.41, 'ECG' 0.64 and 'risk factors' 0.84. Conclusion of the study was that there was very strong overall interoperator reliability. However, the separate components of the HEART score, observer agreement in history and ECG was poor. This was also found in our study. A major difference in the study was that MACE was not an endpoint. Only acute myocardial infarction was reported as outcome in the total group (nine patients, (10%)) and the HEART scores of those patients were not reported. Therefore, no comparison about safety of HEART score risk classification by nurses versus doctors was possible.

Since this study aims to compare two 'real-life' HEART scores in two different settings, there were several baseline differences. For example time of inclusion, type of troponin assessment, different training/experience of paramedics and physicians. One of the major differences between a pre-hospital and hospital HEART scores is type of troponin assessment. We do not expect that difference in troponin assessment was the main cause of 11% false negative risk classifications. In only nine false negative patients, the troponin score in the pre-hospital score was lower than in the hospital score (Table

4) and ICC for troponin assessment was 0.82, which is considered good. Despite the number of false negatives in the pre-hospital group, the amount of MACE is comparable in the pre-hospital versus hospital low-risk groups. Moreover, also seven patients in the false positive group experienced MACE.

Strengths Our study has several strengths. First, it is the first study in which a complete HEART score is prospectively performed in the pre-hospital setting and compared with a prospectively assessed hospital HEART score. Also, all HEART score components were assessed and documented based on separate, independent patient dossiers. This study has significant value when the aim is to relocate risk assessment from hospital to pre-hospital setting in the future. Also, including patients of two large hospitals covering rural as well as more densely populated urban areas of the Netherlands makes the results well generalizable. A precondition is that paramedics are trained to operate autonomously. Paramedics in our study were familiar with the HEART score since 2012 and they were additionally trained in assessing the HEART score including troponin assessment before start of this phase of the Famous Triage project.

Limitations Our study had some noteworthy limitations. Despite the simplicity of the HEART score, a complete pre-hospital HEART score was absent in 120 patients (14.6%), mostly due to a missing troponin measurement (72.5%). Hereby, a potential selection bias cannot be fully excluded. Absence of troponin measurements was mainly attributed to device errors of the cobas h232 POC system. Another cause was the inability to obtain blood from the peripheral venous canula. Possibly, newly developed POC systems are more user-friendly and may have fewer errors. Also integration of venous blood sampling in local EMS protocols might better facilitate the ability to perform POC troponin assessment. A general limitation concerned the difference in hospital and pre-hospital troponin measurement. Nineteen percent of pre-hospital troponin measurements scored lower than the hospital troponin. Our previous study showed that POC troponin measurement compared to high-sensitive hospital troponin was more often false negative when measured shortly after symptom onset.[17] Moreover, POC troponin is also less sensitive which correspondingly accounts for part of the lower pre-hospital troponin scores. High sensitive POC troponin assessments have not been developed yet. Possibly, a pre-hospital HEART score assessment including the current POC troponin is not sensitive enough for patients with short duration of complaints. This should be further investigated. Also, it should be investigated whether POC troponin tests with higher sensitivity can further improve pre-hospital risk classification by the HEART score. Last, we did not consider differences in educational status in our analyses. Educational status might have influenced the ability of pre-hospital risk factor assessment more than hospital risk factor assessment.

Future implications of our study In the future, pre-hospital instead of in-hospital risk assessment in suspected NSTE-ACS might be applicable by the pre-hospital HEART score. However, since leaving low-risk patients at home requires very high sensitivity for adverse events there are some points worth mentioning prior to pre-hospital HEART score implementation with subsequent treatment and/or transfer consequences. First, before low-risk patients can be left home, paramedics should receive additional training in HEART score assessment to prevent misclassification. Mainly the history component should be made more generalizable. Use of standardized objective scoring criteria might be helpful, however so far this has not been shown to be effective.[18]

Second, the HEART score predicts only MACEs, which is mainly composed by cardiac events, other potential serious events are not included. Whether a HEART score should be performed in the first place remains to the discretion of the paramedic. Also importantly, paramedics need to evaluate the indication for hospital examination in case of suspicion of a potentially dangerous alternative cause of symptoms. Last, low-risk patients that are no transported to the hospital in the future should have close follow up by their general practitioner. Possibly, a 'care manager' nurse can serve as a bridge between general practitioners and the emergency medical services.[19] In conclusion, prior to implementation of this risk assessment tool, further research on real-life implementation should be performed.

CONCLUSION

In 74% of patients, hospital and pre-hospital risk classification using the HEART score is similar. Incidence of MACE after 45 days follow up was low and comparable between the low-risk pre-hospital and hospital groups. However, paramedics tend to overestimate the history and ECG components of the HEART score and also missed a minority of patients (7%) as intermediate-high risk. Additional training and objective scoring criteria might improve pre-hospital risk classification by paramedics using the HEART score.

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In-hospital healthcare utilization, outcomes and costs in pre-hospital adjudicated low-risk chest pain patients

Dominique N. van Dongen, Jan Paul Ottervanger, Rudolf Tolsma, Marion Fokkert, Aize van der Sluis, Arnoud W.J. van 't Hof, Erik Badings, Robbert J. Slingerland

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ABSTRACT

Background There is increasing evidence that in patients presenting with acute chest pain, pre-hospital triage can accurately identify low-risk patients. It is, however, yet unclear which diagnostics are performed in pre-hospital adjudicated low-risk patients and what the contribution is of those diagnostic results in the healthcare process.

Objectives The aim of this study is to quantify health care utilization, costs and outcomes in pre-hospital adjudicated low-risk chest pain patients, and to extrapolate to total costs in the Netherlands.

Methods This was a prospective cohort study including 700 patients with suspected non-ST-elevation acute coronary syndrome in which pre-hospital risk stratification using the HEART score was performed by paramedics. Low risk was defined as a pre-hospital HEART score ≤ 3. Data on (results of) hospital diagnostics, costs and discharge diagnosis were collected.

Results A total of 172 (25%) patients were considered as low risk. Of these low-risk patients, mean age was 54 years, 52% were male, 84% of patients were discharged within 12 h. Repeated electrocardiography and routine laboratory measurements, including cardiac markers were performed in all patients. Chest X-ray was performed in 61%, echocardiography in 11% of patients. After additional diagnostics, two patients (1.2%) were diagnosed as non-ST-elevation myocardial infarction and two patients (1.2%) as unstable angina. Other diagnoses were atrial fibrillation (n=1) and acute pancreatitis/cholecystitis (n=2), all other patients had non-specific/non-acute discharge diagnoses. Mean in-hospital costs per patient were €1580. The estimated yearly acute healthcare costs in low-risk chest pain patients in the Netherlands are €30,438,700.

Conclusion In low-risk chest pain patients according to pre-hospital risk assessment, acute healthcare utilization and costs are high, with limited added value. Possibly, if a complete risk assessment can be performed by ambulance paramedics, acute hospitalization of the majority of low-risk patients is not necessary which can lead to substantial cost reduction.

INTRODUCTION

The Netherlands is one of the top spenders on healthcare in the Organization for Economic Cooperation and Development (OECD), spending 10.1% of gross domestic product (GDP) to healthcare.[1] Healthcare spending growth results largely from an increase in the volume of care. Most developed and transitional countries are facing similar challenges, including an aging population, an increase in the prevalence of chronic illnesses and rising expenditures.[2–4]

In the Western world, with its high prevalence of coronary artery disease, chest pain is a common reason for emergency department presentation and early risk assessment is essential to ensure fast treatment in high-risk patients[5]. Risk stratification is nowadays already possible before hospital admission and clear recommendations about risk stratification protocols are available.[5,6] However, while guidelines plea for a short time interval to diagnostics and treatment in high-risk patients[5], no specific recommendations in low-risk patients are given. Possibly, the majority of the pre-hospital identified low-risk patients do not need immediate additional diagnostics. It is, however, yet unclear what the diagnostic costs and their added value in pre-hospital adjudicated low-risk patients are. The aim of the current study was to quantify acute healthcare utilization, diagnostic added value and costs in those low-risk chest pain patients.

METHODS

Study Design and Population This prospective, observational, cohort study, the second phase of the Famous Triage project[7,8], was performed between January 2016 and July 2017. Patients from Deventer hospital and Isala, which are secondary and tertiary care hospitals in the Netherlands, were included. The study involved 33 emergency medical services (EMS) vehicles from two regional ambulance services (RAV IJsselland and Witte Kruis ambulancezorg) staffed by approximately 110 paramedics.

The original aim of the second phase of the Famous Triage project was to determine the accuracy of risk stratification by paramedics using the HEART score (History, Electrocardiogram, Age, Risk factors, Troponin, Figure 1) in patients with suspected non-ST-elevation acute coronary syndrome (NSTE-ACS). The HEART score is a validated risk stratification tool for patients with suspected NSTE-ACS. The aim of the current study was to characterize acute health care utilization and associated costs in pre-hospital adjudicated low-risk chest pain patients.

Figure 1 HEART score

HEART score			
History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥ 65 years	2	
	> 45 and <65 years	1	
	≤ 45 years	0	
Risk factors*	≥ 3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin	≥ 3x normal limit	2	
	1-2 x normal limit	1	
	Normal limit or lower	0	
		Total	

Asterisk indicates risk factors: hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, BMI > 30kg/m^2

ECG electrocardiogram; *HEART* History, ECG, Age, Risk factors, and initial Troponin; *LBBB* left bundle branch block; *PM* pacemaker.

The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The inclusion criteria were out-of-hospital patients aged ≥ 18 years who were attended by an ambulance with a pre-hospital suspicion of NSTE-ACS at first medical contact. The exclusion criteria were pregnancy, comatose state, cognitive impairment, shock, cardiac asthma, sustained ventricular tachyarrhythmia, end stage renal disease, an obvious non-cardiac cause for chest complaints or a strong suspicion of aortic dissection or pulmonary embolism. The study was registered in the Dutch Trial Register [http://www.trialregister.nl]: trial number 4205.

Clinical Assessment Before the start of this study, all paramedics were trained in assessing the HEART score. Prior to inclusion, all patients underwent routine assessment including a brief history, monitoring of vital signs, 12-lead electrocardiogram (ECG) and intravenous access, according to local EMS protocols. The HEART score was fully assessed by paramedics including a fourth generation point-of-care (POC) troponin measurement. Cardiac troponin is a protein found in cardiac muscle fibers that is released into the blood when heart injury occurs. ECG analysis was conducted by

paramedics without use of a computer interpretation program. In the case of uncertainty, the paramedics were able to contact a cardiologist and send the ECG digitally. After HEART assessment and registration, patients were presented to the emergency cardiac-care unit and further treatment was given according to usual care protocols. Low-risk meant a low risk for major adverse cardiac events (MACE) within 45 days, which was defined by a HEART score ≤ 3. This cutoff value was determined and validated by the instigators of this score[9,10]. MACE included acute coronary syndrome, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or death by any cause.

Diagnostic Adjudication Adjudication of the final diagnosis was performed by applying current guidelines and the third universal definition of myocardial infarction[5,11,12]. Acute coronary syndrome was defined as ST-elevation myocardial infarction (STEMI), which was determined by ECG judgement, non-ST-elevation myocardial infarction (NSTEMI) and unstable angina. A PCI was defined as a percutaneous strategy of therapeutic intracoronary balloon dilatation and/or stent placement. CABG was defined as a surgical procedure of coronary artery grafting to bypass a coronary stenosis.

Follow Up and Endpoints Medical records were studied to identify discharge diagnoses and used diagnostics. When there was no in-hospital follow up after 45 days, patients were contacted by telephone or via the patient's general practitioner to identify MACE. Data about used diagnostics during admission and observation duration was extracted by using System Query Language (SQL) in Isala and collected by medical record study in Deventer hospital. A prolonged length of observation was considered an observation period of more than 4 h. This was based on local experience that history taking, complete physical examination and laboratory measurements can be performed within 4 h at the emergency department, and this cut-off point is also used in reimbursement determination by health insurance companies. Costs of diagnostic procedures were based on rates as provided by the Dutch Healthcare authority (NZA) of 2012[13] and 2013.[14] Total costs of ED visits and hospital admission (including facility and professional costs) per patient were given in means for the total group. An extrapolation to calculate the national healthcare expenditures was performed based on the Dutch ambulance care reports and costs determined by NZA.[15–18]

Statistical Analysis Statistical analysis was performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR). Variables were tested for normality of distribution. For the comparison of normally distributed variables a *t* test was used to compare means, for non-normally distributed

variables a non-parametric variant (Mann - Whitney *U* test) was used. Categorical variables were reported by frequencies and percentages and were compared with chi-square test. To test for variables associated with prolonged observation, multivariable analyses were performed using logistic regression model. A *p* value of ≤0.05 was considered statistically significant.

Patient Involvement The medical ethical committee included a representative of patients. Patient priorities were considered, but no patients were involved in development of the research protocol. However, the protocol was funded by the Isala Research Fund and approved by a committee which included two participants of the patient council of Isala hospital.

RESULTS

From January 2016 to July 2017 a total of 823 patients were considered eligible by paramedics. A total of 703 patients (83%) had a complete HEART score of which 700 patients (99.6%) had complete follow up. A total of 174 (25%) of those patients had a pre-hospital HEART score of ≤ 3 and were therefore considered low risk. Two (1%) low-risk patients had missed follow up. Patient characteristics of low- versus intermediate-high-risk patients are shown in Table 1. The mean age (SD) of the total population was 64 (± 14) years; the mean age of the 172 low-risk patients was 54 (±12) years.

Median observation duration in the low-risk group was 4.6 h (IQR 3.2 – 6.7), mean observation duration was 17.9 (± 53.6) h. In 107 patients (62%) observation duration was prolonged. A total of 144 patients (84%) were discharged within 12 h. Seventeen patients (10%) had prolonged observation, while the onset of complaints was more than 6 h prior to inclusion.

Median complaint duration prior to inclusion was 2.7 h (IQR 1.5 – 6.8) in the low-risk group. Patients with a short observation period had a significantly longer duration of complaints at the time of inclusion compared to patients with a prolonged observation period: 4.3 (IQR 2.0 – 9.5) h versus 2.2 (IQR 1.4 – 4.4) h ($p < 0.001$). Subsequently complaint duration of < 6 h prior to inclusion was significantly associated with prolonged observation (OR 4.55, 95% 2.22 – 9.09, $p < 0.001$). Patient characteristics (age, gender, cardiac risk factors, cardiac history) were not significantly associated with prolonged observation. Table 2 shows the diagnostic procedures performed and the corresponding costs per diagnostic procedure. In 61% of all patients, chest radiography was performed. Eleven percent underwent echocardiography of which one patient (2%) had a short observation period.

Table 1 Patient characteristics of patients with low risk (HEART ≤ 3) versus intermediate-high risk (HEART > 3) as classified by pre-hospital risk assessment.

Variable	Low Risk (n = 172)	Intermediate- high Risk (n = 528)	P value
Age (years)	54 (±12)	67 (±13)	< 0.001
Men (%)	86 (50%)	315 (60%)	0.026
Diabetes Mellitus	9 (5%)	111 (22%)	< 0.001
Body mass index ≥ 30kg/m2	33 (28%)	107 (25%)	0.502
Hypercholesterolemia*	46 (27%)	229 (45%)	< 0.001
Hypertension^	62 (37%)	310 (60%)	< 0.001
Positive family history of CAD	77 (46%)	247 (48%)	0.588
Current smoker	44 (26%)	112 (22%)	0.264
Previous AMI	13 (8%)	137 (26%)	< 0.001
Previous PCI	13 (8%)	162 (31%)	< 0.001
Previous CABG	2 (1%)	64 (12%)	< 0.001
Previous TIA/Stroke	2 (1%)	41 (8%)	0.002
Previous Peripheral artery disease	2 (1%)	29 (6%)	0.017
Elevated POC troponin	1 (1%)	68 (13%)	< 0.001
Duration of complaints, h median IQR	2:40 (1:31 -6:48)	3:00 (1:35 – 8:16)	0.18
Onset of complaints > 6h before inclusion	47 (27%)	164 (31%)	0.354
Second in-hospital troponin assessment	104 (60%)	314 (59%)	0.817

Values are n (%) or mean ± SD.

CAD coronary artery disease, AMI acute myocardial infarction, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, TIA transient ischemic attack; POC point of care NSTEMI non-ST-elevation myocardial infarction

*Hypercholesterolemia refers to patients receiving lipid-lowering therapy

^ Hypertension refers to patients receiving blood pressure medication

There was no significant relationship between patient characteristics and additional cardiac diagnostics (echocardiography, coronary CT angiography/calcium score, exercise electrocardiography, coronary angiography).

A second troponin measurement was performed significantly more often in the prolonged observation group (81% versus 31%, $p < 0.001$) and was a significant predictor for prolonged observation (OR 8.22; 95% CI 4.08 – 16.55; $p < 0.001$). Symptom duration of < 6 h was a significant predictor of second troponin assessment (OR 4.61; 95% CI 2.27 – 9.09; $p < 0.001$). In multivariate analysis both complaint duration <6 h (OR 2.86; $p = 0.009$) and second troponin assessment (OR 6.55; $p < 0.001$) were significant predictors for prolonged observation. No patient characteristics were significantly associated with second troponin assessment.

Table 2 Diagnostics procedures and costs in 172 low-risk patients as classified by pre-hospital triage

	Low risk N = 172	Costs per patient, €		Total cost within group, €
Observation duration and costs	N (%)	Mean (SD)	Median (IQR)	
Short observation	65 (38%)	537 (± 404)	482 (303- 482)	34,905
Prolonged observation	107 (62%)	1920 (± 2224)	1400 (1400 – 1400)	205,440
Total observation costs		*1397 (± 1965)*		*240,345*
Diagnostic tests and costs	N (%)	Costs per test, €		
Blood testing	172 (100%)	55		9460
ECG	172 (100%)	34		5848
Second troponin	104 (61%)	9		936
X-thorax	105 (61%)	52		5460
Echo	18 (11%)	74		1332
Coronary CT Angiography	1 (1%)	299		299
Coronary Calcium Score	1 (1%)	205		205
Exercise electrocardiography	8 (5%)	98		784
Coronary Angiography	9 (5%)	789		7101
Total diagnostic costs		*183*		*31,425*
Total costs		1581		271,770

Table 3 shows the discharge diagnoses. The majority of patients had non-specific thoracic complaints (90%). In hospital, nine (5%) of patients were diagnosed with stable angina. Four patients (3%) experienced a MACE within 45 days (two NSTEMI, two unstable angina). There were no life-threatening events (i.e., ventricular arrhythmias, hemodynamic instability, acute interventions) during hospitalization in the total low-risk group.

Mean diagnostic costs in the low-risk group were €183 per patient. Mean observation costs (including facility and professional costs) were €1397 euro per patient. The yearly amount of urgent ambulance deployments is 973.000 in the Netherlands and 24% of these deployments is for a cardiac reason.[17] In Isala, the percentage of emergency department cardiac-care presentations for suspected NSTE-ACS was 33% in 2016. Considering the expected amount of low-risk patients identified by paramedics using the HEART score is 25% of chest pain patients, the estimated number of yearly low-risk chest pain patients is 973.000 x 24% x33% x 25% = 19.265 patients. By extrapolating these results, the annual in-hospital costs for low-risk chest pain patients in the Netherlands are approximately € 30,438,700.

Table 3 Discharge diagnoses after hospital diagnostics in 172 low-risk chest pain patients as classified by pre-hospital triage

Diagnosis	Total N = 172
NSTEMI	2 (1.2%)
Unstable angina	2 (1.2%)
Atrial fibrillation	1 (0.6%)
Stable angina	9 (5.2%)
Cholecystitis	1 (0.6%)
Pancreatitis	1 (0.6%)
Pericarditis	1 (0.6%)
Non-specific thoracic complaints	155 (90.1%)

DISCUSSION

We demonstrated that in pre-hospital adjudicated low-risk chest pain patients, costs for healthcare utilization are high, with limited added diagnostic value. This is the first study that estimated in-hospital diagnostics and costs in patients with suspected NSTE-ACS that underwent pre-hospital risk assessment.

Several previous studies investigated diagnostics or costs after in-hospital risk assessment of chest pain patients.[19–22] Comparing the number of additional diagnostics in the low-risk group in our study to a low-risk group in a previous Dutch study (as determined by the HEART score) [22], exercise testing (5% vs. 32%) and echocardiography (11% vs. 17%) were performed less often in our study. Scintigraphy was not performed in either study, coronary angiography was performed equally often (5% of patients). The number of chest X-rays and blood testing performed adjacent to troponin assessment in chest pain patients had not previously been clearly reported in other studies. The hospital observation period was shorter and the admission/hospitalization rate lower in our study than in low-risk patients in previous studies[20,23]. Reasons for these differences can be patient selection, variation in hospital protocols, waiting time for adjacent diagnostics, or the use of high-sensitive troponin in our study instead of lower sensitive troponin in other studies. It is also possible that the pre-hospital diagnostics in our study resulted in less hospital diagnostics.

The limited added value of additional diagnostics and observation management in low-risk chest pain patients was suggested previously.[24,25] Probably, these patients can be discharged safely in the short term, with only limited additional diagnostics.[9,24,26] However, current guidelines are not clear about diagnostics in these low-risk patients. European

Society of Cardiology (ESC) guidelines note that stress testing can be performed in patients with negative biomarkers and nonischemic ECGs, and that, in patients with low to intermediate likelihood for NSTE-ACS, computed tomography (CT) coronary angiography should be considered when no other chest pain-explaining alternative conditions are found.[5] However, the evidence of these recommendations is low (only expert opinion). Our study shows that the only predictors for prolonged observation are onset of complaints within 6 h of submission and troponin assessment. This is consistent with the current guidelines, which recommend a second troponin assessment when complaints started within 6 h of admission.[5] Since troponin assessment is possible at home, this is an unnecessary reason for emergency department presentation. Furthermore, there were no variables significantly associated with additional diagnostics. A recent study comparing 293,788 patients who received no initial non-invasive test with 127,986 patients who underwent initial non-invasive testing, found no difference in the risk of myocardial infarction at day 7 or day 190.[19] Furthermore, while hospitals vary in their use of additional diagnostics, rates of therapeutic interventions or readmission do not differ substantially.[27] This confirms the suggestion that in the future, hospitalization of low-risk patients might not be necessary anymore. However, it also raises questions about why some low-risk patient undergo further diagnostics, could this be doctor driven?[25,28,29]

Mean hospital costs including emergency department and clinical admission costs in our study were comparable with a previous Dutch study[22]; €1490 versus €1397 in our study. The mean and median show that costs were skewed to the right (Table 2) which is a common phenomenon in cost reports.[30,31] Because we expect that there will always be cost-intensive patients that have effect on the total costs that are needed over time, we used mean costs to extrapolate to overall costs. Median costs do not provide information about the costs of treating all patients, which is needed as the basis for healthcare policy decisions.[30,31]

Additional diagnostic costs were not completely comparable. The previous Dutch study reported mean costs of €125 for exercise testing, echocardiography and coronary angiography. In our study, also chest X-ray, adjacent blood testing and CT coronary angiography were also taken into account for adjacent diagnostic cost calculation, which resulted in mean costs of €183. A recent study that was performed in the United States reported median hospital costs of US$ 1921 (€1700) in patients with clinical evaluation only and US$ 2475 (€2190) in patients with clinical evaluation and noninvasive testing.[23] Although this shows considerable variation, both costs are noticeably high, particularly in this low-risk population.

Given the high volume of patients presenting with chest pain, national healthcare costs in low-risk patients are substantial. We estimated the in-hospital costs for low-risk chest pain patients in the Netherlands at € 30,438,700 annually. Considering the concern about the growing healthcare costs[3], and keeping in mind that diagnostics are often performed without substantial evidence, without clear recommendation in the guidelines and with limited additional value, avoidance of hospitalization of low-risk chest pain patients may give an opportunity to restrict further growth in healthcare spending.

Strengths Our study had several strengths. Firstly, it is the first prospective study to asses a complete HEART score, including troponin assessment in the pre-hospital setting. Secondly, we had data on all diagnostics performed during the hospital observation period. Thirdly, we had almost complete follow up (172/174 patients, 99%), including clinical events.

Limitations Our study had some noteworthy limitations. A complete HEART score was absent in 120 patients of 823 patients (14.6%), mostly due to a missing POC troponin result (87 patients, 73% of missing HEART scores). Hence, the existence of selection bias cannot be fully excluded. Also, although the HEART score is partly validated with 4th generation troponin assessments[9,10], high sensitive POC troponin test may have resulted in better predictive value of HEART. This study describes acute healthcare utilization and costs; however, it is possible that patients underwent adjacent consulting and tests after hospital discharge. Lastly, the sample size of our study was too small to perform analyses of subgroups.

Future implications of our study Considering that in-hospital HEART score decision models already may reduce healthcare utilization and costs[20,22,32], pre-hospital HEART score implementation can further decrease healthcare utilization in low-risk chest pain patients leading to a more efficient healthcare system. Whether routine patient admission is actually a beneficial strategy in low-risk chest pain can be questioned. In view of safety, it should be kept in mind that currently in the Netherlands 20% of all patients attended by an ambulance are not transferred to an emergency department.[17] So far, the incidence of MACE in those patients is unknown. Furthermore, in primary care, only 1.5 – 3.6% of the patients who present with thoracic complaints have an acute coronary syndrome[33], and the majority are not immediately referred to a hospital.[34,35] Future, larger studies should assess the risk of not transporting low-risk chest pain patients before this can be recommended in the guidelines.

CONCLUSION

The majority of pre-hospital adjudicated low-risk chest pain patients experience prolonged hospital observation and a number of additional diagnostics with limited added value. This is associated with high costs, which may be in part unnecessary. Further research is needed to assess whether pre-hospital triage of chest pain patients is safe and can help to avoid unnecessary costs.

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8

Pre-hospital troponin as predictor of early revascularization in suspected NSTE-ACS

Dominique N. van Dongen MD, Rudolf T. Tolsma, MSc, Arnoud W.J. van 't Hof MD PhD, Erik A. Badings MD PhD, Marion J. Fokkert, ing, Aize van der Sluis, MD, Robbert J. Slingerland, PhD, Jan Paul Ottervanger, MD PhD

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ABSTRACT

Introduction Previous studies showed the efficacy of a pre-hospital HEART score in risk classification of patients at low risk for suspected NSTE-ACS. Predictors of revascularization within this pre-hospital group have not yet been assessed. In this study we investigated whether patients with elevated pre-hospital troponin are at high risk for early revascularization, and compared this with the pre-hospital HEART score.

Methods This is a prospective cohort study including 1289 consecutive patients with suspected NSTE-ACS in which pre-hospital risk stratification using the HEART score including point-of-care troponin was performed by paramedics. Patient characteristics, HEART score and point-of-care troponin assessment were compared in multivariate logistic regression analyses. Endpoint was revascularization (either PCI or CABG) within 30 days of inclusion.

Results A total of 99 patients (8%) had elevated troponin, 180 patients (14%) had high-risk HEART score (≥7), 165 patients (13%) received revascularization within 30 days. A total of 49 (49%) of patients with elevated troponin received revascularization (univariate OR 8.7 95% CI 5.6 – 13.5, after multivariable analyses OR 7.5 95% CI 4.7 – 11.9). Of the patients with high-risk HEART score, 52 (29%) received revascularization (OR 3.6 95% CI 2.5 – 5.3).

Conclusion Elevated pre-hospital troponin is the strongest predictor for early revascularization in patients with suspected NSTE-ACS and possibly, those patients benefit from direct transfer to a PCI center. Future studies should focus more on identification tools for patients at high risk for revascularization.

INTRODUCTION

Pre-hospital risk stratification by paramedics using the HEART score including point-of-care troponin is feasible in patients with suspected NSTE-ACS.[1] So far, studies have mainly focused on identification of low-risk patients and the necessity of immediate treatment or adjacent diagnostics in this group.[1,2] Until now, identification of high-risk patients with suspected NSTE-ACS is performed in the hospital. However, pre-hospital identification of patients at high risk for revascularization may possibly shorten time to treatment. Moreover, the HEART score was also intended for identification of high-risk patients.[3] This study aims to investigate whether predictors for revascularization can be identified in a pre-hospital setting.

METHODS

Study design and population This prospective observational study contains the first and second phase of the Famous Triage project.[4,5] The first phase was performed between June 2012 and December 2014, the second phase was performed between January 2016 and July 2017. Patients from Isala and Deventer Hospital were included which are tertiary and secondary care hospitals in the Netherlands. The study involved approximately 33 emergency medical services vehicles from 2 regional ambulance services (Ambulance IJsselland and Witte Kruis ambulancezorg) staffed by circa 110 paramedics. The original aim of the first and second phase of the Famous Triage project was to determine the accuracy of risk stratification by paramedics in patients with suspected NSTE-ACS.[1,4] The aim of the current study was to assess whether risk stratification by a pre-hospital HEART score including 4th generation troponin is suitable for the identification of patients receiving revascularization within 30 days. The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committees.

The inclusion criteria were out-of-hospital patients with age ≥ 18 years, visited by an ambulance with a pre-hospital suspicion of NSTE-ACS at first medical contact. The exclusion criteria were pregnancy, comatose state, cognitive impairment, shock, cardiac asthma, sustained ventricular tachyarrhythmia, end stage renal disease, an obvious non-cardiac cause for chest complaints or a strong suspicion of aortic dissection or pulmonary embolism. The study was registered in the Dutch Trial Register [http://www.trialregister.nl]: trial number 4205.

Pre-hospital assessment Prior to the start of this study, all paramedics were trained in determining the HEART score. The HEART score is shown in figure 1. Preceding inclusion, all patients underwent routine assessment including a brief history, monitoring of vital signs (blood pressure, heart rate, pulse oximetry), 12-lead electrocardiogram and intravenous access, according to local emergency medicine service protocols. Pre-hospital HEART score assessment by paramedics was described previously[1]. In the first phase a pre-hospital blood sample was derived after insertion of a venous line and analysed in the hospital laboratory. In the second phase a pre-hospital cardiac troponin T assay was performed on site using the Roche CARDIAC POC troponin T test on the cobas h 232 POC system with a detection range of 40 – 2000 ng/L. POC test results were available in 8 – 12 minutes. The HEART score was originally validated with both 4th generation and high sensitive troponin assays[3]. Originally 1 point was given when troponin was elevated between 1-3 times the upper reference limit and 2 points when troponin was elevated ≥ 3 times the upper reference limit despite the sensitivity of troponin assessment. In the current study a troponin value below 40ng/L scored 0 points and a troponin value exceeding 40 ng/L scored 2 points. This scoring was determined by using the abovementioned HEART score criteria with high sensitive troponin cut-off points for the point of care troponin, which has a limit of detection of 40ng/L.

All blood that was derived was collected to assess cardiac troponin T at the clinical chemistry laboratory using the hs-cTnT Modular and Cobas 8000 system of Roche Diagnostics, Manheim, Germany, with a limit of detection of 3 ng/L and inaccuracy corresponding to a 10% coefficient of variation at the 99th percentile upper reference limit (URL) of the reference population. For endpoint adjudication, a hs-cTnT value exceeding the 99th percentile URL (14 ng/L) was considered elevated. Low-risk was defined as a HEART score ≤ 3.

Diagnostic adjudication Adjudication of the final diagnosis was performed by applying current guidelines and the third universal definition of myocardial infarction.[6–8] Cardiac ischemia was defined as ST-segment elevation myocardial infarction (STEMI), which was determined by ECG judgement, non-ST-segment elevation myocardial infarction (non-STEMI) and unstable angina. Non-STEMI diagnosis was made when the in-hospital cardiac high sensitive troponin value was above the 99th percentile upper reference limit (14 ng/mL) with a significant delta after serial sampling with 3 hours interval as well as ECG judgement and a clinical setting consistent with myocardial ischemia. Unstable angina was diagnosed as a clinical setting consistent with myocardial ischemia and normal cardiac high sensitive troponin or above the 99th percentile upper reference limit without a significant delta. All other patients were diagnosed with stable angina, non-cardiac chest pain or cardiac but non-coronary disease (e.g., tachyarrhythmias, heart

failure). A percutaneous coronary intervention (PCI) was defined as a percutaneous strategy of therapeutic intracoronary balloon dilatation and/or stent placement. A CABG was defined as a surgical procedure of coronary artery grafting as to bypass a coronary stenosis.

Figure 1 HEART score

HEART score			
History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥ 65 years	2	
	> 45 and <65 years	1	
	≤ 45 years	0	
Risk factors*	≥ 3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin°	≥ 3x normal limit	2	
	1-2 x normal limit	1	
	Normal limit or lower	0	
		Total	

* Risk factors: Hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, BMI > 30kg/m²

° POC troponin below 40ng/L was scored 0, values exceeding 40 ng/L scored 2 points. Hospital troponin was scored according this figure.

ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; PM = pacemaker.

The outcome was revascularization within 30 days of inclusion. To identify revascularization, medical record studies were performed. When there was no in-hospital follow up, patients were contacted by telephone or via the patient's general practitioner.

Patient involvement The medical ethical committee included a representative of patients. Patient priorities were considered, but no patients were involved in development of the research protocol. However, the protocol was funded by the Isala Research Fund and approved by a committee which included two participants of the patient council of Isala hospital.

Statistical analysis Statistical analysis was performed using IBM SPSS statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA) and R (R Core Team, 2018). Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR). Variables were tested for normality of distribution. For the comparison of normally distributed variables a t test was used to compare means, for non-normally distributed variables a non-parametric variant (Mann - Whitney U test) was used. Categorical variables were reported by frequencies and percentages and were compared with chi-square test. To study the association between patient characteristics and revascularization, logistic regression analyses were performed with revascularization (yes/no) as outcome measure and included separately to study univariate associations with revascularization. Outcomes are presented as odds ratios with 95% confidence intervals. Subsequently, multivariate regression analyses were performed with all univariate associated characteristics. A p-value of ≤ 0.05 was considered statistically significant.

RESULTS

A total of 1300 patients were deemed eligible by paramedics (600 patients in phase 1, 700 patients in phase 2). In 11 patients (0.8%) troponin results were missing. Further inclusion information was published previously.[1,5]

Patient characteristics are shown in table 1. Mean age of the total group was 63 years (SD ±14), 58% was male. Prevalence of smoking was 23%, hypertension 49%, and a history of prior PCI 25%. 99 Patients (8%) had elevated POC troponin. Patients with elevated POC troponin were significantly older, more often male and had more often diabetes. 49 patients (49%) with elevated troponin received revascularization. Sensitivity of elevated pre-hospital troponin for revascularization was 30%, specificity 96%. AUC was 0.62 (95% CI 0.57 – 0.68).

180 Patients (14%) were considered at high-risk according the HEART score (table 2). The intermediate to high risk HEART score patients were older, more often male, had a significantly higher prevalence of cardiovascular risk factors and significantly more often prior atherosclerotic diseases. Prevalence of revascularization was 52 (29%) in the high-risk HEART score group. Sensitivity for revascularization within the high-risk HEART score group was 32%, specificity was 89%. AUC was 0.60 (95% CI 0.55 – 0.65).

Table 1 Patient characteristics and type of revascularization in patients with versus without elevated pre-hospital troponin

Characteristics	Total group N = 1289	Normal pre-hospital troponin n = 1190 (92%)	Elevated pre-hospital troponin n = 99 (8%)	P value
Mean age, y (SD)	63.4 (14)	61.5 (13.9)	74.4 (9.1)	< 0.001
Male, n (%)	743 (58%)	674 (57%)	69 (70%)	0.012
Cardiac risk factors, n (%)				
Diabetes Mellitus	214 (17%)	185 (16%)	29 (29%)	< 0.001
Obesity (body mass index ≥ 30kg/m2)	172 (13%)	158 (13%)	14 (14%)	0.998
Hypercholesterolemia	438 (34%)	404 (34%)	34(34%)	0.856
Hypertension	631 (49%)	584 (49%)	47 (47%)	0.895
Current smoking	298 (23%)	273 (23%)	25 (25%)	0.507
History of cardiovascular disease, n (%)				
Acute myocardial infarction	258 (20%)	236 (20%)	22 (22%)	0.568
Previous revascularization	325 (25%)	294 (25%)	31 (31%)	0.146
Cerebrovascular accident or transient ischemic attack	60 (5%)	50 (4%)	10 (10%)	0.007
Type of Revascularization				
PCI	109 (8%)	76 (6%)	33 (33%)	< 0.001
CABG	56 (4%)	40 (3%)	16 (19%)	< 0.001

Table 3 shows the prevalence and odds ratio after univariate logistic regression analysis of patient characteristics in patients with versus without revascularization. Age, male gender, troponin, ECG abnormalities, HEART score, hypercholesterolemia, previous myocardial infarction and previous revascularization were all significantly associated with revascularization. After multivariate regression analyses, male gender (OR 2.5 95% CI1.7 – 3.8, p < 0.001), elevated POC troponin (OR 7.5 95% CI 4.7 – 11.9, p < 0.001), ECG abnormalities (OR 3.1 95%CI 1.8 – 5.1, p < 0.001) and hypercholesterolemia (OR 1.5 95% CI 1.0 – 2.2, p = 0.028) were still significant predictors of revascularization with elevated POC troponin being the strongest predictor for revascularization. Multivariate analyses with high-risk HEART and male gender resulted in an OR of 3.5 (95% CI 2.4 – 5.2, p < 0.001) OR 2.6 (95% CI 1.8 – 3.8), p < 0.001), respectively.

Table 2 Patient characteristics and type of revascularization in patients with low-intermediate versus high risk according pre-hospital HEART score

Characteristics	Low-intermediate risk n = 1109 (86%)	High risk n = 180 (14%)	P value
Mean age, y (SD)	61.5 (13.9)	74.4 (9.1)	<0.001
Male, n (%)	629 (57%)	114 (63%)	0.096
Cardiac risk factors, n (%)			
Diabetes Mellitus	149 (13%)	65 (36%)	<0.001
Obesity (body mass index ≥ 30kg/m2)	144 (13%)	28 (16%)	0.529
Hypercholesterolemia	362 (33%)	76 (42%)	0.007
Hypertension	527 (48%)	104 (59%)	0.007
Current smoking	273 (25%)	25 (14%)	0.002
History of cardiovascular disease, n (%)			
Acute myocardial infarction	192 (17%)	66 (37%)	<0.001
Previous revascularization	236 (21%)	89 (49%)	<0.001
Cerebrovascular accident or transient ischemic attack	38 (3%)	22 (12%)	<0.001
Type of Revascularization			
PCI	78 (7%)	31 (17%)	<0.001
CABG	35 (3%)	21 (12%)	<0.001

DISCUSSION

The aim of this prospective observational study was to investigate whether pre-hospital risk assessment is feasible to identify patients with suspected NSTE-ACS at high-risk for early revascularization. It was demonstrated that the predictive value of elevated pre-hospital point-of-care troponin is high since half of patients with elevated POC troponin received revascularization within 30 days. After multivariate analyses elevated point-of-care troponin showed the highest association with early revascularization.

There are a few studies that investigated the use of POC troponin in a pre-hospital setting. Especially studies of Terkelsen *et al.*, focused on pre-hospital identification and risk assessment in suspected NSTE-ACS with help of pre-hospital POC troponin. In a recent study it was concluded that identification of NSTE-ACS patients in the pre-hospital setting was feasible and appeared to facilitate early diagnosis and treatment.[9] In a previous study, POC troponin also showed feasibility in identification of patients with the highest risk in the pre-hospital setting.[10] Another study also showed that it was feasible to diagnose NSTE-

ACS patients in the pre-hospital phase by help of POC troponin and/or ECG results and that subsequent acute coronary angiography may impact the mode of revascularization and results in significant reduction in length of hospital stay and a highly significant reduction in time-to-CAG and –revascularization.[11] A limitation for the comparison of this study with our study was that in 32% patients POC troponin was not assessed and there was no direct analysis on the results of POC troponin with revascularization.

Beside pre-hospital studies, there are several in-hospital studies on risk assessment in suspected NSTE-ACS. For example TIMI and GRACE risk scores were developed to identify NSTE-ACS patients at high risk for major adverse cardiac events that might benefit from early invasive diagnostics and/or treatment.[12,13] Several recent studies showed that the ESC hs-cTn 0/1h algorithm is efficient and safe for rule-out and rule-in of NSTEMI[14–16] and that it shows a 'powerful and reliable risk stratification of short-term and long-term risk of mortality and MACE'.[17] This last cited study showed a positive predictive value for NSTEMI of 68% for hospital hs-TnT ≥ 52 ng/L. In our study, elevated pre-hospital POC troponin meaning troponin ≥ 40 ng/L showed a PPV for revascularization of 49%. A major difference between all abovementioned studies and our study is that these studies mainly focused on diagnosis of suspected NSTE-ACS and timing of coronary angiography in patients with diagnosed NSTE-ACS whereas the aim of our study was to identify predictors of revascularization in a pre-hospital setting. Future studies should assess whether a pre-hospital POC troponin of >52 ng/L shows a comparable predictive value. It also might be interesting to perform sub analyses in the beforementioned studies to assess the predictive value for revascularization.

Strengths Our study has several strengths. First, this is the first study in which pre-hospital POC troponin is compared with pre-hospital HEART scoring. Second this is the first study assessing the predictive value of pre-hospital POC troponin and HEART scoring for revascularization. We had follow up of almost all patients. This study has significant value when the aim is to improve risk assessment in a pre-hospital setting in the future and potentially has direct implications for treatment of patients with pre-hospital elevated POC troponin.

Limitations Our study also had some noteworthy limitations. Since the HEART score was missing in some patients[1] we cannot fully exclude a selection bias either caused by paramedics or the POC device. The sample size of our study was too small to perform subgroup analyses. Possibly, pre-hospital risk stratification is not suitable in patients with short duration of complaints. This should be further investigated. Lastly, we only used POC troponin T and high sensitive troponin T. Clinical significance of the results is therefore limited to these specific assays and cannot be generalized to other cardiac troponin assays.

Table 3 Univariate analyses on characteristics of 1289 patients with versus without revascularization within 30 days

	Revascularization N=165
	N=165 (13%)
Mean age (SD), y	63 (14)
<45 years	6 (4%)
45-65 years	73 (45%)
≥ 65 years	85 (52%)
Male, n (%)	125 (76%)
Pre-hospital Troponin > 40ng/L	48 (29%)
Pre-hospital Troponin > 14 ng/L	112 (68%)
ST-deviation or new T wave inversion	32 (20%)
HEART ≤ 3	10 (6%)
HEART 4 – 6	102 (62%)
HEART ≥ 7	52 (32%)
Cardiac risk factors, n (%)	
Diabetes Mellitus	32
Obesity (body mass index > 30kg/m2)	22
Hypercholesterolemia	69 (%)
Hypertension	80
Current smoking	45
History of cardiovascular disease, n (%)	
Acute myocardial infarction	43 (26%)
Previous revascularization	54 (33%)
Cerebrovascular accident or transient ischemic attack	4 (2%)

Future implications of our study So far, guidelines and studies mainly focused on rule-in and rule-out of acute coronary syndrome and on identification of high-risk NSTE-ACS patients. The current ESC guideline on NSTE-ACS advises to transfer high and very high-risk patients to a PCI center within 24 hours to perform invasive testing at very short term[6]. However, based on our results, the benefit of direct transfer and/or invasive testing of high-risk HEART score patients can be questioned. The mean age of this group was 74 years and half of patients had previous revascularization which may result in complex procedures or conservative treatment. Possibly, the decision on transfer to a PCI center should not be based on patient characteristics like age, kidney function or risk factors, but on criteria as ECG and troponin since these are most associated with revascularization in our study. Moreover, possibly the term 'high risk' should refer more to high risk for revascularization instead of high risk for

No revascularization N = 1124	**Odds ratio**	**P value**
N = 1124 (87%)		
66 (12)	1.017 (1.005 – 1.03)	0.004
119 (11%)	0.321 (0.139 – 0.741)	0.005
495 (44%)	1.021 (0.734 – 1.420)	0.902
511 (45%)	1.293 (0.931 – 1.795)	0.124
618 (55%)	2.632 (1.802 - 3.831)	< 0.001
51 (5%)	8.714 (5.622 – 13.506)	< 0.001
261 (23%)	7.130 (4.990 – 10.187)	< 0.001
79 (7%)	3.210 (2.049 – 5.028)	< 0.001
312 (28%)	0.169 (0.088 – 0.325)	< 0.001
685 (61%)	1.057 (0.754 – 1.481)	0.749
128 (11%)	3.610 (2.481 – 5.263)	< 0.001
182	1.231 (0.811 – 1.869)	0.329
150	0.923 (0.569 – 1.497)	0.745
369	1.445 (1.034 – 2.018)	0.030
551	0.976 (0.703 – 1.356)	0.885
253	1.281 (0.884 – 1.857)	0.19
215 (19%)	1.504 (1.030 – 2.196)	0.034
271 (24%)	1.547 (1.087 – 2.202)	0.015
56 (5%)	0.477 (0.171 – 1.334)	0.149

mortality, myocardial infarction or other adverse events. Based on our study, elevated POC troponin can be considered an indicator for direct transfer to a PCI center to minimize time to treatment, length of stay and consecutive healthcare utilization. Possibly, future studies should focus more on identification tools for patients at high risk for revascularization.

CONCLUSION

Half of patients with suspected NSTE-ACS and elevated pre-hospital POC troponin receives revascularization at short term. Possibly, patients with elevated pre-hospital POC troponin should be transferred to a PCI center.

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9

Referral decisions based on a pre-hospital HEART score in suspected non-ST-elevation acute coronary syndrome: design of the Famous Triage 3 study

D.N. van Dongen, R.T. Tolsma, M.J. Fokkert, E.A. Badings, A. van der Sluis, R.J. Slingerland, A.W.J. van 't Hof, E. van 't Riet, J.P. Ottervanger

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ABSTRACT

Background It is not yet investigated whether referral decisions based on pre-hospital risk stratification of non-ST-elevation Acute Coronary Syndrome (NSTE-ACS) by the complete History, ECG, Age, Risk factors and initial Troponin (HEART) score are feasible and safe.

Hypothesis Implementation of referral decisions based on the pre-hospital acquired HEART score in patients with suspected NSTE-ACS is feasible and not inferior to routine management in the occurrence of major adverse cardiac events within 45 days.

Study design & methods Famous Triage 3 is a feasibility study with a before–after sequential design. The aim is to assess whether pre-hospital HEART score management including point-of-care troponin measurement is feasible and noninferior to routine management. Primary endpoint is the occurrence of major adverse cardiac events within 45 days.

Conclusion If referral decisions based on pre-hospital acquired risk stratification are feasible and noninferior this can become the new pre-hospital management in suspected NSTE-ACS.

INTRODUCTION

Early risk stratification of chest pain patients can improve treatment management by rapid identification of patients at high risk and avoidance of unnecessary diagnostics in low-risk patients.[1–6] There is growing evidence that in patients with suspected non-ST-elevation Acute Coronary Syndrome (NSTE-ACS), pre-hospital risk assessment is feasible and has comparable accuracy to in-hospital risk assessment.[1,3,7–9] Several studies also showed that additional diagnostics in low-risk patients lead to a longer length of stay and higher costs without reduction of clinical events.[5,6,10,11] By pre-hospital risk stratification, treatment decisions can be made faster. History, ECG, Age, Risk factors and initial Troponin (HEART)-score calculation (Table 1), including point-of-care (POC) troponin assessment, has demonstrated to be feasible for pre-hospital use by paramedics.[1,9,12,13] It adequately stratifies patients in low-, intermediate- and high risk for MACE.[3,14,15] In phase 1 and 2 of the Famous Triage study, the pre-hospital acquired HEART score was incorporated in routine patient assessment, without treatment consequences.[3,16] In the current described phase 3 of Famous Triage, paramedics will use a pre-hospital acquired HEART score for treatment decisions. It is the first study in which chest pain patients at low risk for NSTE-ACS will be observed at home.

STUDY DESIGN AND METHODS

Study design Famous Triage 3 is a non-inferiority, controlled before-after multicenter study with a sequential design with the aim to assess feasibility and safety of pre-hospital risk assessment by paramedics using the HEART score. The study will be performed in Deventer and Isala hospital which are secondary and tertiary care hospitals in the Netherlands. The study involves 33 emergency medical services vehicles from 2 regional ambulance services (RAV IJsselland and Witte Kruis ambulancezorg) staffed by approximately 110 paramedics which are registered nurses, specialised in pre-hospital care. An overview is given in figure 1. In Famous Triage 2[16], a pre-hospital HEART score including point-of-care (POC) troponin was prospectively assessed by paramedics without treatment consequences. These patients are in the control (before) group. In the treatment (after) group, a HEART score is calculated in the same way, but patients with a HEART score of ≤3 are asked to give informed consent to be analyzed at home instead of being transferred to the hospital. In those patients, a second HEART score will be assessed at home 3-12 hours after inclusion (Figure 2). The reason for a second reassessment is that previous results showed that patients that are included shortly after onset of complaints might have false negative troponin results[16]. When patients are left home, their general practitioner is informed and patients are instructed by

the paramedic to contact their general practitioner to investigate the cause of their complaints, particularly when complaints persist. Patients with a HEART score of > 3 are transferred to a nearby hospital.

Table 1 HEART score

HEART			
History (anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicous	0	
ECG	Significant ST-segment deviation	2	
	Nonspecific repolarization disturbance/LBBB/PM	1	
	Normal	0	
Age	≥ 65 years	2	
	> 45 and <65 years	1	
	≤ 45 years	0	
Risk factors*	≥ 3 risk factors or history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No known risk factors	0	
Troponin	≥ 3x normal limit	2	
	1-2 x normal limit	1	
	Normal limit or lower	0	
		Total	

* Risk factors: Hypercholesterolemia, hypertension, diabetes mellitus, cigarette smoking, family history of atherosclerotic disease, BMI > 30kg/m^2

ECG = electrocardiogram; HEART = History, ECG, Age, Risk factors, and initial Troponin; LBBB = left bundle branch block; PM = pacemaker.

Point of care Troponin A cardiac troponin T assay will be performed on site using the Roche CARDIAC POC troponin T test on the cobas h 232 POC system with a limit of detection of 40 – 2000 ng/l. The device is able to work properly in a temperature range from 18 to 32 °C, a relative humidity of 10–85 % (no condensation) and maximum altitude of 4300 m. The POC testing strips are sustainable for 7 days after removal from the refrigerator. POC test results are available in 8 – 12 minutes.

Study population The inclusion criteria are out-of-hospital patients aged ≥ 18 years visited by an ambulance with a pre-hospital suspicion of NSTE-ACS. The exclusion criteria are electrocardiographic ST-elevation, pregnancy, comatose state, cognitive impairment, shock, cardiac asthma, ventricular tachyarrhythmia, endstage renal disease, an obvious non-cardiac cause for complaints or a strong suspicion of either aortic dissection or pulmonary embolism.

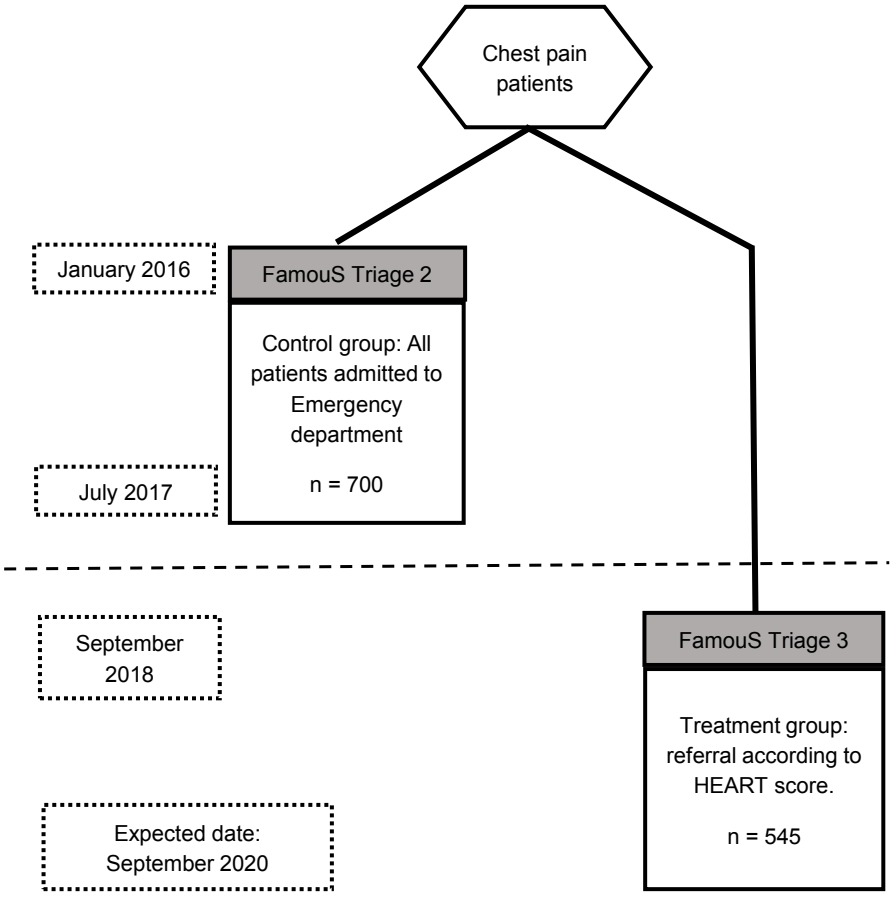

Figure 1 Overview of inclusion of cohorts

Study hypothesis and endpoints Our hypothesis is that referral decisions based on the pre-hospital HEART score in patients with suspected NSTE-ACS are feasible and non-inferior to routine management according to the current guidelines4 in the occurrence of MACE within 45 days. The primary endpoint is the occurrence of MACE within 45 days of inclusion. MACE consists of the following events: Myocardial infarction, unstable angina, PCI, CABG, death by all causes. Adjudication of the final diagnosis will be performed by applying current guidelines and the third universal definition of myocardial infarction.4,17–19 ST-segment elevated Myocardial Infarction (STEMI) will be determined by ECG judgement. Non-STEMI diagnosis is adjudicated when high-sensitive cardiac troponin value is above the 99th percentile upper reference limit (URL) with a significant delta (≥ 20%) as well as a clinical setting consistent with myocardial ischemia. Unstable angina is diagnosed when there is a clinical setting consistent

with myocardial ischemia and high-sensitive cardiac troponin is normal or above the 99th percentile URL without a significant delta. All cases with possible endpoints are reviewed by 2 independent adjudicators without knowledge of the HEART score. In case of disagreement, the case is discussed in a plenary adjudication committee meeting, composing at least two cardiologists that are not related to the study, until consensus is reached.

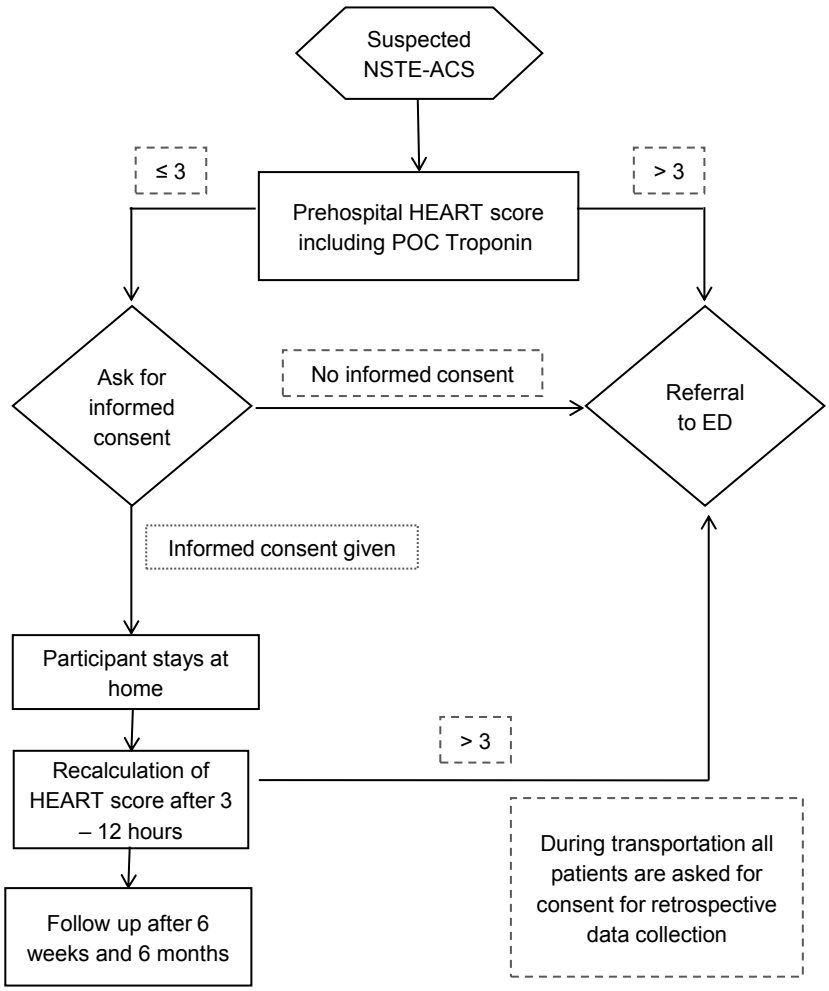

Figure 2 Flow chart of patient inclusion

Major secondary outcome measures are feasibility, the occurrence of death or ACS within 30 and 45 days of inclusion and potential predictors of coronary revascularization within 45 days in the high-risk group.

Additional secondary outcome measures are the added value of a second HEART score assessment in low-risk patients, the occurrence of MACE within 6 months of inclusion, the number of patients that are secondarily referred to the hospital for cardiac reasons with a HEART score of ≤3 within 6 months after inclusion, discharge diagnosis of all patients either primarily or secondarily referred to the hospital within 6 months after inclusion, the number of inter-hospital transfers between PCI and non-PCI centers, length of hospital stay, performed diagnostics, healthcare costs, reimbursement costs and cause of death.

Follow up Patients will be contacted three months after inclusion to detect possible endpoints and to make an inventory of used healthcare recourses. A follow up duration of 45 days is chosen because the HEART score was validated to predict MACE within 6 weeks and to allow enough time for patients to visit their general practitioner and undergo additional diagnostics. Any information that indicates possible endpoints will be further investigated through hospital charts and information obtained from general practitioners. After 6 months, hospital patient dossier study for possible endpoints and outcome measures will be performed. Also, the Municipal Personal Records Database will be consulted for information on vital status. An overview of follow up and data collection is given in figure 3.

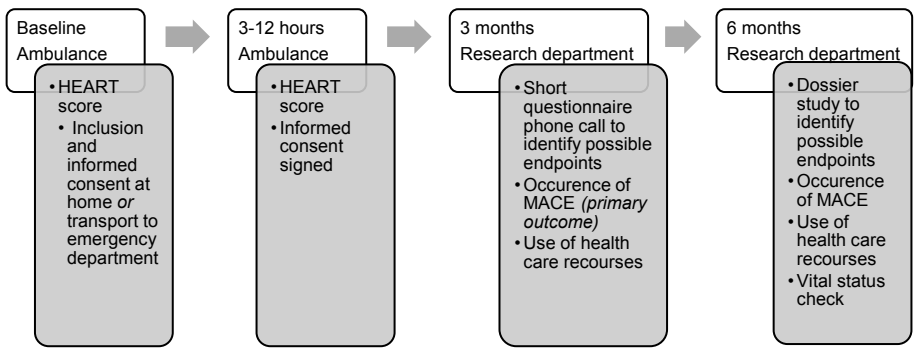

Figure 3 Overview of data collection and follow up Phase 3

STATISTICAL ANALYSIS

Primary analysis Primary analysis is aimed to study whether pre-hospital HEART-management will not cause more MACE than routine management. The primary outcome is the absolute difference in MACE incidence rate between the control and treatment group.

Secondary analyses Because of the design of the study there may be differences in baseline characteristics due to a discrepancy in the time of enrolment. Hence, we may have to account for potential confounding and selection biases. Cox regression model, with proportion of MACE as outcome, type of population as primary determinant and time to MACE as time at risk, will be used to estimate hazard ratios and adjust for confounding factors. Potential confounding factors will be included in the model. Hazard ratios with 95% confidence interval of the fully adjusted model will be presented. Determinants and confounding factors included in the analyses for major primary and secondary endpoints are shown in Table 2

To assess the occurrence of either death or ACS within 45 days of inclusion, we will determine the percentage of patients with an ACS or death within 45 days of inclusion in both groups. To assess feasibility, the total number of pre-hospital adjudicated low-risk patients will be determined and compared to the number of secondary transfers within the group and the number of patients that refused informed consent to be analyzed at home. Also the number of POC device failures or other difficulties in assessing the HEART score will be analyzed. To study the association between patient characteristics and PCI, we will perform a logistic regression analysis, with PCI (yes/no) as outcome measure. Patient characteristics of patients included in phase 2 and phase 3 with a HEART score ≥ 7 will be included into the model separately to study univariate associations with referral.

Table 2 Determinants and confounding factors included in the analyses for major primary and secondary endpoints

Analyses	**Primary outcome**
Cox regression	MACE within 45 days Death or ACS within 30 and 45 days
Logistic regression	PCI within 45 days

Outcomes will be presented as odds ratios with 95% confidence intervals. Multivariate regression will be performed in which all univariately associated characteristics are included. A backwards regression model, using -2log likelihood, will be used to optimize a model with highest proportion of the total variance in referral explained by the model.

Sample size The aim of this study is to assess whether pre-hospital referral decisions (treatment group) according the HEART score is feasible and does not lead to an increase in MACE within 45 days of presentation compared to routine management (control group). Our sample size calculation is therefore based on demonstrating that the proportion of MACE in the treatment group is non-inferior to the proportion observed in the control group. Preliminary results of the second phase of Famous Triage showed 15.7% (13.1-18.6) MACE.[16] Available guidelines for choosing a non-inferiority-margin are mainly based on comparing two pharmaceutical interventions, and choosing a non-inferiority-margin based on the effect estimate of one of those pharmaceutical interventions compared to placebo in earlier research (M1) and the preserved fraction of M1 (M2), usually set at 50%.[20,21] Since a comparison to placebo does not apply to our research design, we used the expected incidence of 15.7% as the point estimate (meaning no difference between control and intervention) and set the non-inferiority-margin at 7.5%. This is comparable to other research in which two non-pharmaceutical interventions are compared.[22–26] Non-inferiority will be declared if the upper limit of the one-sided 97.5% CI of the absolute risk difference (ARD) between the treatment group and control group is not greater than 7.5% (Figure 4). If there is truly no difference in incidence of MACE between the control and treatment groups, then a total amount of 990 patients is required to be 90% sure that the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will exclude a difference in favour of the control group.[27,28] The expected number of patients with loss of follow up or missing data is 10%. Therefore, the total sample size will be at least

Primary determinant	Confounding factors	Predictors
HEART score	Gender	-
-	-	Patient characteristics: Age Gender POC troponin Risk factors HEART score

1090 (545 in each group). The control group, composed of Famous phase 2, consists of 700 participants. In phase 3, at least 545 participants will be included conform the presented sample size. If we, for feasibility reasons, will not be able to include the same amount of participants as in phase 2, a random selection of the phase 2 participants will be performed for the comparison statistics.

Figure 4 Interpretation of the noninferiority margin. Δ presents the noninferiority margin, in this study noninferiority will be declared if the upper limit of the one-sided 97.5% CI of the ARD between the treatment group and control group is not > 7.5%.This figure presents the interpretation and conclusion of the noninferiority marging in different study outcomes.

ARD: Absolute risk difference.

Regulation statement This study is conducted according to the principles of the current declaration of Helsinki and in accordance with 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 Isala clinics, Zwolle, the Netherlands, METC No.170526), and subsequently by the boards of the participating hospitals.

PRESENT STATUS

Famous Triage phase 2 was performed from January 2016 until July 2017. Famous Triage phase 3 started September 2018 and is expected to finish in September 2020. So far, 350 patients were included. The study is investigator driven and supported by an Isala I&W grant. POC materials are sponsored by Roche Diagnostics. The authors are responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

DISCUSSION

Famous Triage is the first study in which the complete HEART score is investigated in a pre-hospital setting.[2,3,9] The first observational phase of this study was performed with retrospective HEART assessment and hs-TnT.[3] The second observational phase was performed with a complete pre-hospital HEART score, including POC TnT assessment[16] and showed that pre-hospital risk-assessment is safe. This third, implementation, phase is performed to evaluate feasibility and safety of pre-hospital HEART-treatment.

Contrary to multiple studies on pre-hospital diagnostics and treatment in suspected STEMI, there are only few studies that investigate pre-hospital risk assessment and treatment in suspected NSTE-ACS. Two studies showed that an elevated pre-hospital POC TnT is highly predictive of mortality in patients with a suspected acute myocardial infarction.[13,29] In one study, pre-hospital POC TnT measurement detected 39% of all patients with acute myocardial infarction with an AUC of 0.67.[13] Another study showed an AUC of 0.68[1] for POC TnT diagnosing NSTEMI. Our previous results show that the AUC for detecting MACE with a pre-hospital HEART score is 0.74.[16] It seems that pre-hospital troponin assessment without clinical assessment is particularly useful in identifying patients at high risk, but it is less suitable for identification of patients at low risk. Another study showed added value in fast identification of NSTEMI by on-scene echocardiography by an emergency physician.[30] However, in most countries an emergency physician is not present in first response ambulance teams. Moreover, this approach also identifies high-risk patients that might benefit from fast transfer to an interventional center. It does not identify low-risk patients that can be analyzed at home. Lastly, a recent study showed added value in identification and fast treatment of high-risk patients by e-transmission of ECG's for expert consultation.[31] Again, this approach improves identification of high-risk patients and does not aim to identify low-risk patients.

Strengths and limitations Our study has several strengths. First it is the first prospective study on implementation of pre-hospital HEART score referral decision making. Patients in the area of 2 large hospitals, covering rural as well as more densely populated urban areas of the Netherlands, will be included which makes the results well generalizable. The study simulates pre-hospital HEART score implementation in future guidelines as closely as possible. A precondition is that paramedics have been trained to operate autonomously. In the Netherlands, ambulance paramedics have bachelor degrees in nursing with at least 2 subsequent specialisations in critical care nursing. Paramedics in our study are familiar with the HEART score since 2012 and they were additionally trained in assessing the HEART score including troponin assessment before start of this phase of the Famous Triage project.

There are also some limitations. In order to comply with the current non-STEMI guideline, which recommends a second troponin measurement when complaints started within 6 hours, a second HEART score including troponin measurement will be performed. This might reduce previous anticipated cost benefits and efficient healthcare resource use. However, the original HEART score validation studies did not assess a second troponin measurement.[15,32] Therefore, a secondary outcome measure of this study is to assess whether a second HEART score in low-risk patients is necessary for excluding MACE within 45 days of inclusion. Furthermore, it is important to realize that the HEART score is developed to assess the risk of MACE within 45 days. It does not assess the risk of other potential dangerous causes of chest complaints. An obvious non-cardiac cause for chest complaints or strong suspicion of aortic dissection or pulmonary embolism are exclusion criteria. Paramedics in the Netherlands are well trained in clinical assessment and it remains to the discretion of paramedics whether a patient should be referred to the hospital or not regardless of the HEART score. Also, it is possible that paramedics in other healthcare systems are less highly educated and require additional training before this pre-hospital approach can be implemented.

It is also important to emphasize that the aim of this study is to evaluate feasibility of pre-hospital HEART score referral decision making and to assess whether implementation of this approach is non-inferior to standard management. However, this study has a before-after sequential design in which in both study groups the HEART score is prospectively assessed. Therefore, it is important to be aware of bias and correct for potential confounders. When pre-hospital HEART score decision making appears to be feasible and non-inferior compared to standard management this can become future standard management. A fourth, randomized controlled trial must be performed to prove safety of this new approach, before guidelines can be changed unless a high sensitive point of care troponin becomes available. In that case pre-hospital and hospital troponin assessment have similar sensitivity.[33]

Future implications Through early identification of patients who in fact need neither (cardiology) admission nor hospital evaluation, unnecessary transfer can be avoided. This can reduce healthcare expenditures, which is an important focus for improvement of the current healthcare system.[34–36] Another point of interest is pre-hospital identification of high-risk patients in need of acute revascularization which can lead to direct transfer to an interventional center with consequent reduction of time to treatment. The current ESC non-STEMI guideline emphasizes a more aggressive strategy in high-risk patients with non-STEMI.[4] It is recommended that very high-risk patients should receive a coronary angiography within two hours and patients with a non-STEMI and elevated troponin or high GRACE score should receive a coronary angiography within 24 hours. This is more likely to be accomplished with pre-hospital identification of these patients.

SUMMARY

The Famous Triage 3 study is the first study which will assess whether pre-hospital referral decision making using the HEART score in patients with suspected NSTE-ACS is feasible and safe. The results of this study can be a stepping stone towards improved pre-hospital management with reduced costs and improved outcomes in patients with suspected NSTE-ACS.

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10

Summary, conclusions and future perspectives

SUMMARY AND CONCLUSIONS

Until now, complete risk stratification in patients with suspected NSTE-ACS is performed in the hospital. However, since point-of-care troponin assessment has been developed, risk stratification is nowadays also performable outside the hospital. This thesis addresses the feasibility of pre-hospital risk stratification in suspected NSTE-ACS. The goals of this thesis were to investigate how low-risk patients can be accurately identified by paramedics, to assess the healthcare utilization in those patients and to evaluate whether patients at high-risk for revascularization can be identified.

In **chapter 1**, a brief introduction about the subject and the background of the thesis is given. Suspected NSTE-ACS is a common reason for emergency department presentation and requires fast risk stratification. Further research is needed to assess whether risk stratification with subsequent treatment decisions is feasible in the pre-hospital setting.

The first phase of the Famous Triage research project is reported in **chapter 2**. This was the first study in which paramedics assessed a pre-hospital HEART score. In 600 patients with suspected NSTE-ACS the HEAR components of the HEART score were prospectively assessed by paramedics. Blood samples were collected at time of inclusion and troponin assessment was performed in the hospital. A total of 140 patients (23%) were classified as low, 341 (57%) as intermediate and 119 (20%) as high-risk patients. Occurrence of MACE within 30 days was 3%, 19% and 45%, respectively ($p < 0.001$). There were no deaths in the low-risk group. AUC of the pre-hospital HEART score for predicting MACE was 0.77 (95% CI 0.73 – 0.81). The importance of this study lies primarily in proving the feasibility of pre-hospital HEAR(T) scoring by paramedics.

For the second phase of the Famous Triage research project, a pre-hospital point-of-care troponin was introduced in the ambulance. **Chapter 3** describes the main outcomes of this study. In 700 patients with suspected NSTE-ACS risk stratification was performed by paramedics. A total of 172 patients (25%) were stratified as low risk and 528 patients (75%) as intermediate to high-risk. MACE occurred in 5 patients in the low-risk group (3%) and in 111 (21%) patients at intermediate or high risk ($p < 0.001$). There were no deaths in the low-risk group and the occurrence of acute myocardial infarction in this group was 1%. In the high-risk group 6 patients died (1%) and 76 patients had myocardial infarction (14.4%). Conclusion was that pre-hospital risk stratification by paramedics is accurate, but to decrease MACE in the low-risk group further training of paramedics and a second troponin assessment when measurement was shortly after complaint onset are needed.

In **chapter 4** we assessed the added value of the troponin component to the HEART score. Mean HEAR score was 4.5 ± 1.6, mean HEART score was 4.7 ± 1.7. Using the HEAR score, a total of 183 patients (26%) were stratified as low risk, whereas using the HEART score, 172 patients (25%) were stratified as low risk (p = 0.001). In both low-risk groups, there were no deaths within 45 days. Using HEAR, MACE occurred in 13 patients (7%) in the low-risk group, whereas using HEART, MACE occurred in 5 patients in the low-risk group (3%, p <0.001). The use of HEART (AUC 0.74) obtained a higher predictive value compared to HEAR (AUC 0.65, p <0.001) for MACE. Conclusion was that in patients with suspected NSTE-ACS, the pre-hospital troponin component of the HEART score has important added predictive value.

Whether a pre-hospital HEART score is equally accurate with using point-of-care or high sensitive troponin is investigated in **chapter 5**. In 689 consecutive patients with suspected NSTE-ACS, point-of-care troponin and laboratory high-sensitive troponin were measured in pre-hospital derived blood. For every patient the HEART score with both point-of-care troponin (HEART-POC) and high sensitive troponin (HEART-hsTnT) was determined. 163 (24%) Patients were considered low-risk by using HEART-hsTnT and 170 (25%) by using HEART-POC. Although high sensitive versus POC troponin scoring was different in 130 (19%) of patients, in 678 (98%) patients risk classification in low versus intermediate-high risk was similar. The predictive values of HEART-POC versus HEART-HsTnT was also similar (AUC 0.75 versus 0.76, p = 0.241). Conclusion was that POC troponin measurement suffices for pre-hospital risk stratification in suspected NSTE-ACS.

Because the HEART score was originally validated in the hospital setting we compared the pre-hospital HEART score with the in-hospital HEART score in **chapter 6**. In 699 patients with suspected NSTE-ACS, the HEART score was independently prospectively assessed in the pre-hospital setting by ambulance paramedics and in the hospital by physicians. In 516 (74%) patients pre-hospital and hospital risk classification was similar, in 50 (7%) pre-hospital risk classification was false negative (45 days mortality 0%) and in 133 (19%) false positive (45 days mortality 1.5%). Occurrence of MACE was comparable in pre-hospital and hospital low-risk patients (2.9% versus 2.7%, p = 0.9). Predictive values of both pre-hospital and hospital acquired HEART scores were high, although the AUC of hospital acquired HEART score was higher (0.84 vs 0.74, p <0.001). Disagreement was primarily caused by different scoring of history and risk factors and therefore additional training may improve pre-hospital scoring.

If low-risk patients do not need to be transferred to the hospital anymore in the future, there might be a reduction in healthcare utilization (and costs). In **chapter 7** we assessed the diagnostics in pre-hospital low-risk patients and the contribution of those

diagnostic results in the healthcare process. 84% of patients was discharged within 12 hours. Repeated electrocardiography and routine laboratory measurements, including cardiac markers were performed in all patients. Chest X-ray was performed in 61%, echocardiography in 11% of patients. After additional diagnostics, 2 patients (1%) were diagnosed as non-STEMI, 2 patients (1%) as unstable angina. Other diagnoses were atrial fibrillation (n=1) and acute pancreatitis/cholecystitis (n=2), all other patients had non-specific/non-acute discharge diagnoses. Mean in-hospital costs per patient were €1.580. The estimated yearly acute healthcare costs in low-risk chest pain patients in the Netherlands are €30.438.700.

Beside early identification of low-risk patients, pre-hospital risk assessment could also facilitate faster identification of high-risk patients. In **chapter 8** we investigated whether patients at high risk for early revascularization can be identified in a pre-hospital setting. This was a prospective cohort study including 1289 consecutive patients with suspected NSTE-ACS in which the HEART score including point-of-care troponin was performed by paramedics. Endpoint was revascularization (PCI or CABG) within 30 days of inclusion. A total of 164 patients (13%) received revascularization within 30 days. Of 99 patients (8% of total group) with elevated point-of-care troponin, 49 (49%) received revascularization. Of 180 patients (14%) with high-risk HEART score, 52 (29%) received revascularization. Both elevated troponin (OR 8.7) and high-risk HEART score (OR 3.6) were significantly associated with revascularization after univariate analysis. After multivariate regression analysis elevated point-of-care troponin remained the strongest predictor for revascularization. Possibly, patients with elevated point-of-care troponin benefit from direct transfer to a PCI center.

Until now, all research has been observational. Pre-hospital risk assessment and troponin results have not been implemented in pre-hospital treatment decisions. Because the previous mentioned studies showed feasibility of pre-hospital risk assessment, phase 3 of the Famous Triage study was initiated. In **chapter 9** the rationale and design of this phase are reported. The aim is to further assess whether pre-hospital HEART score management including point-of-care troponin measurement and subsequently not transferring low-risk patients to the hospital is feasible and non-inferior to routine management.

FUTURE PERSPECTIVES

The main subject of this thesis was pre-hospital risk assessment in patients with suspected non-ST-elevation acute coronary syndrome. The results show that this approach is feasible and probably results in significant cost reductions considering the amount of diagnostics that is performed in low-risk patients. Although these findings provide good prospects, our studies had several limitations including a limited sample size and a non-randomized design. Additional research with larger patient groups and with a randomized design is needed before pre-hospital risk assessment can be implemented in ambulance and possibly general practitioner guidelines. This research has great societal relevance, considering the high prevalence of cardiovascular risk factors including diabetes and hypertension worldwide and due to the aging of the population it is expected that the amount of patients with suspected NSTE-ACS will increase in the future.

Patients with suspected NSTE-ACS represent a large and heterogeneous group in which fast risk assessment and following treatment decisions are crucial. The challenge to make the healthcare process in those patients more efficient is faced since decades and substantial progress is already made for example by accelerated and improved laboratory assessments, development of international risk assessment protocols and digitalization of healthcare. In suspected NSTE-ACS, both identification of low-risk patients and high-risk patients have fastened since laboratory turnaround time and sensitivity of laboratory assessments have improved noticeably. The in- and exclusion of NSTE-ACS by troponin protocols have fastened from a 6h protocol to 3h or even 1h protocols. However, there are still several ways to improve healthcare in suspected NSTE-ACS.

Place and timing of risk assessment in suspected NSTE-ACS So far, risk assessment in suspected NSTE-ACS is performed between the hospital walls. Considering the results that were reported in this thesis, it can be questioned whether low-risk patients should actually be transferred to the hospital. However to prove non-inferiority of pre-hospital risk assessment compared to hospital risk assessment, further research is mandatory. Nonetheless, already several improvements can be made.

As mentioned, (serial) troponin assessment is a keystone for in- and excluding NSTE-ACS. This parameter often takes the longest time in the risk assessment process. Until now, patients are first transported to the hospital and installed in a hospital bed before blood withdrawal takes place. Afterwards this blood is assessed in the hospital laboratory and troponin results are available after approximately 45-60 minutes. To

decrease time to troponin results, blood can already be withdrawn in the ambulance. If this pre-hospital withdrawn blood is directly sent to the laboratory upon arrival, this could safe approximately 30-45 minutes. Moreover, if a second troponin measurement is needed this can be performed considerably earlier.

Following, also ECG assessment is already performed in the ambulance and upon arrival in the hospital, this ECG is available for the physician as first risk assessment information. Since the ECG is digital information, this could be sent forward to the patients electronic patient file which facilitates earlier hospital risk assessment.

Earlier treatment decisions Like many other studies, this thesis mainly speaks about risk for disease. However, the primary endpoint of the HEART score is major adverse cardiac events (MACE). This endpoint comprises both physical conditions: acute coronary syndrome and death, as well as treatment: revascularization. The potential benefit of pre-hospital risk stratification comes from transfer decisions. The reason for transferring a patient or not is mainly based on the need for (hospital) treatment. Leaving a low-risk patient at home is feasible because this patient does not need immediate hospital diagnostics or treatment. Identification of high-risk patients should also be based on the need for diagnostics and treatment. So far, in hospital risk scores are often based on risk for myocardial infarction or risk for mortality. However, beside advise on observation time on the critical care unit and advise on timing of coronary angiography (if appropriate), no concrete recommendations follow. Therefore, future risk calculators or clinical prediction rules should focus more on risk for treatment. A patient at high risk for mortality may not benefit from direct transferal to a PCI center whereas a patient at high risk for revascularization does.

Future troponin assessment Fast diagnostics are essential for early treatment decisions. With the current point-of-care troponin devices a 'so-called' improved fourth generation troponin is measured within 10-12 minutes. Because this assessment is not sensitive enough to detect elevated troponin shortly after onset of complaints, a second assessment will remain necessary. And even then, the test will not be as sensitive as the high-sensitive troponin assays that are nowadays used in the hospital.

Because of the increased sensitivity of laboratory troponin, clinical rule-in and rule-out ACS protocols have fastened significantly. Numerous studies on direct rule-in and rule-out were performed and have shown that ACS in patients with very low or non-detectable levels of high-sensitivity troponin can safely be ruled-out. The current point of care troponin assessments are by far not sensitive enough for this oh approach and to meet up with the rapidly developing clinical approach more sensitive point-of-care

troponin devices are necessary. Conversely, also the rule-in approach has fastened significantly and patients with suspected NSTEMI and a troponin >52 ng/L at 0h or delta troponin of ± 5 ng/L after 1h seem to be eligible for early coronary angiography for rapid detection and revascularization of culprit lesions. The current point-of-care troponin can be pre-hospitally used for this rule-in approach in patients with a troponin ≥40 ng/L.

Worth mentioning is that all diagnostic algorithms should always be used in conjunction with clinical assessment of vital signs, risk factors, the 12-lead ECG and chest pain characteristics. Troponin-only based treatment decisions should be avoided.

Transmural care Elaborating on the transmural care by cooperation and data exchange between ambulance and hospital, there could also be an essential role for general practitioners. Beside the patients that are transferred to the hospital by ambulance, there is also an important amount of patients with thoracic complaints visiting the general practitioner. When complaints are suspicious for NSTE-ACS, general practitioners refer their patients to the hospital for fast risk stratification. However, also general practitioners can perform a HEART score including troponin assessment. That way, the referral of a substantial amount of patients can possibly be avoided. Moreover, if there is a high suspicion of NSTE-ACS and point-of-care troponin is elevated and/or ECG is notably abnormal, patients can be transported to the hospital more rapidly. For beneficial cooperation between all healthcare professionals, in- and outside the hospital, easy communication methods, rapid and safe information exchange and 'transmural' reimbursement are essential.

Healthcare reimbursement Pre-hospital risk stratification with subsequent treatment decisions can result in significant cost reductions for example by avoidance of unnecessary transfer of low-risk patients and by possibly shorter hospital stay of high-risk patients. This can be one of the methods to restrict further growth in healthcare spending. However, more profound cost analyses including long term costs and effect on general practitioner visits, referrals and diagnostics are needed.

One of the bottlenecks of the transmural approach in this thesis is the current healthcare financing structure. So far, only hospital care that is performed in the hospital is reimbursed by the healthcare insurance. Pre-hospital risk assessment is, with exception of local (pilot) projects, generally not financed. Moreover, if low-risk patients are not being transferred to the hospital in the future, hospitals will actually lose income when the current reimbursement structure is maintained.

The future hospital We expect that the future hospital will be significantly different from the hospital as we know it today. In the first place because of demographic changes of the entire society but also because hospital care will become increasingly centralized. Low-risk patients will be identified pre-hospitally and will be referred to first line care. Patients that are submitted to the general hospitals will be older, be more vulnerable and will have more comorbidities. Hospital stays will be replaced by outpatient treatment as soon as feasible. High-risk patients that need specialized interventions will be more centralized in a limited number of hospitals. Concluding, overall healthcare will become increasingly transmural and hospital walls will figuratively vanish. This thesis addresses an important step to adapt the approach of suspected NSTE-ACS to the future healthcare system.

11

Samenvatting, conclusies en toekomstperspectieven

SAMENVATTING EN CONCLUSIES

Tot nu toe wordt risicostratificatie bij patiënten met een mogelijk non-ST-elevatie acuut coronair syndroom (NSTE-ACS) in het ziekenhuis uitgevoerd. Tegenwoordig bestaat er echter ook 'point-of-care' (POC) troponingebepaling, en daardoor is risicostratificatie hedendaags ook buiten het ziekenhuis uitvoerbaar. In dit proefschrift wordt prehospitale risicostratificatie bij een mogelijk NSTE-ACS uitgevoerd door ambulancemedewerkers onderzocht. De doelen van dit proefschrift waren om te onderzoeken hoe patiënten met een laag risico nauwkeurig kunnen worden geïdentificeerd door ambulancemedewerkers, om het gebruik van de gezondheidszorg bij die patiënten te bepalen en om te evalueren of patiënten met een hoog risico op revascularisatie kunnen worden geïdentificeerd.

In **hoofdstuk 1** wordt een korte introductie gegeven over het onderwerp en de achtergrond van het proefschrift. Verdenking op NSTE-ACS is een veel voorkomende reden voor verwijzing naar de spoedeisende hulp en vereist snelle risicostratificatie. Verder onderzoek is nodig om te beoordelen of risicostratificatie met daaropvolgende behandelbeslissingen haalbaar is in de prehospitale setting.

De eerste fase van het Famous Triage-onderzoeksproject wordt beschreven in **hoofdstuk 2**. Dit was de eerste studie waarin ambulancemedewerkers een HEART score pre-hospitaal bepaalden. Bij 600 patiënten met verdenking op NSTE-ACS werden de HEAR-componenten van de HEART score prospectief beoordeeld door ambulancemedewerkers. Bloedmonsters werden bij presentatie prehospitaal afgenomen en de troponinemeting werd uitgevoerd in het ziekenhuis. In totaal 140 patiënten (23%) werden geclassificeerd als laag risico, 341 (57%) als gemiddeld risico en 119 (20%) als hoog risico. Het optreden van MACE binnen 30 dagen was respectievelijk 3%, 19% en 45% ($p < 0{,}001$). Er waren geen sterfgevallen in de laagrisicogroep. De area under the curve (AUC) van de pre-hospitale HEART score voor het voorspellen van MACE was 0,77 (95% CI 0,73 - 0,81). Het belang van deze studie lag voornamelijk in het aantonen van de haalbaarheid van prehospitale HEAR (T) -score door ambulancemedewerkers.

Voor de tweede fase van het Famous Triage-onderzoeksproject is een prehospitale Point-of-Care troponine geïntroduceerd in de ambulance. **Hoofdstuk 3** beschrijft de belangrijkste uitkomsten van dit onderzoek. Bij 700 patiënten met verdenking op NSTE-ACS werd prehospitale risicostratificatie uitgevoerd door ambulancemedewerkers. In totaal 172 patiënten (25%) werden gestratificeerd als laag risico en 528 patiënten (75%) als gemiddeld tot hoog risico. Major adverse events (MACE) traden op bij 5 patiënten in de laagrisicogroep (3%) en bij 111 (21%) patiënten met gemiddeld of hoog risico ($p < 0{,}001$). In de groep met een laag risico traden geen sterfgevallen op en het optreden

van een acuut myocardinfarct in deze groep was 1%. In de hoog-risico groep stierven 6 patiënten (1%) en 76 patiënten hadden een myocardinfarct (14,4%). Geconcludeerd werd dat prehospitale risicostratificatie door ambulancemedewerkers nauwkeurig is, maar ook dat verdere training en een tweede troponinemeting wanneer klachten recent zijn ontstaan zijn nodig om MACE in de laagrisicogroep te verlagen.

In **hoofdstuk 4** werd de toegevoegde waarde van de troponinecomponent van de HEART score onderzocht. De gemiddelde HEAR-score was 4,5 ± 1,6, de gemiddelde HEART score was 4,7 ± 1,7. Met behulp van de HEAR-score werden in totaal 183 patiënten (26%) gestratificeerd als laag risico, terwijl met behulp van de HEART score 172 patiënten (25%) werden gestratificeerd als laag risico (p = 0,001). In beide groepen met een laag risico waren er binnen 45 dagen geen sterfgevallen. Met HEAR trad MACE op bij 13 patiënten (7%) in de laagrisicogroep, terwijl bij gebruik van HEART MACE optrad bij 5 patiënten in de laagrisicogroep (3%, p <0,001). Het gebruik van HEART (AUC 0.74) leverde een hogere voorspellende waarde voor MACE op in vergelijking met HEAR (AUC 0.65, p <0.001). De conclusie was dat bij patiënten met verdenking op NSTE-ACS de prehospitale troponinecomponent van de HEART score een belangrijke toegevoegde voorspellende waarde heeft.

Of een prehospitale HEART score even nauwkeurig is bij het gebruik van point-of-care troponine als bij gebruik van hoog-sensitief troponine wordt onderzocht in **hoofdstuk 5**. Bij 689 patiënten met verdenking op NSTE-ACS werden point-of-care troponine en hoog-sensitief troponine (hsTnT) uit het laboratorium bepaald uit pre-hospitaal verkregen bloed. Voor elke patiënt werd de HEART score met zowel point-of-care troponine (HEART-POC) als met hoog-sensitief troponine (HEART-hsTnT) bepaald. 163 (24%) Patiënten werden als laag risico beschouwd bij gebruik van de HEART-hsTnT en 170 (25%) bij gebruik van de door HEART-POC. Hoewel de T score voor hsTnT versus POC troponine anders was bij 130 (19%) van de patiënten, was bij 678 (98%) patiënten de risicoclassificatie in laag versus middelhoog-hoog risico vergelijkbaar. De voorspellende waarden van HEART-POC versus HEART-HsTnT waren ook vergelijkbaar (AUC 0,75 versus 0,76, p = 0,241). Geconcludeerd werd dat POC troponinemeting volstaat voor pre-hospitale risicostratificatie bij verdenking op NSTE-ACS.

Omdat de HEART score oorspronkelijk is gevalideerd voor gebruik in het ziekenhuis, vergeleken we de prehospitale HEART score met de hospitale HEART score in **hoofdstuk 6**. Bij 699 patiënten met verdenking op NSTE-ACS werd de HEART score onafhankelijk van elkaar prehospitaal bepaald door ambulancemedewerkers, en in het ziekenhuis door artsen. Bij 516 (74%) patiënten was de pre-hospitale en de hospitale risicoclassificatie vergelijkbaar, bij 50 (7%) was de prehospitale risicoclassificatie vals

negatief (45 dagen mortaliteit 0%) en bij 133 (19%) vals positief (45 dagen sterfte 1,5%). Het optreden van MACE was vergelijkbaar bij prehospitale en hospitale patiënten met een laag risico (2,9% versus 2,7%, p = 0,9). De voorspellende waarde van zowel prehospitale als hospitale HEART scores waren hoog, hoewel de AUC van de ziekenhuis HEART score hoger was (0,84 versus 0,74, p <0,001). Het verschil werd voornamelijk veroorzaakt door verschillende scores voor anamnese en risicofactoren. Gesuggereerd werd dat aanvullende training de pre-hospitale score zou kunnen verbeteren.

Als laag-risico patiënten in de toekomst niet meer naar het ziekenhuis hoeven te worden vervoerd, leidt dat mogelijk tot vermindering van het gebruik (en de kosten) van de gezondheidszorg. In **hoofdstuk 7** hebben we de diagnostiek bij prehospitale patiënten met een laag risico en de bijdrage van die diagnostische resultaten aan het zorgproces in kaart gebracht. 84% Van de patiënten werd binnen 12 uur ontslagen. Bij alle patiënten werden standaard electrocardiografie (ECG) en routinematige laboratoriummetingen, inclusief hartenzymen, uitgevoerd. Een röntgenfoto van de thorax werd uitgevoerd bij 61% van de patiënten, echocardiografie bij 11% van de patiënten. Na aanvullende diagnostiek werd bij 2 patiënten (1%) de diagnose non-ST-elevatie myocardinfarct gesteld en bij 2 patiënten (1%) instabiele angina pectoris. Andere diagnoses waren atriumfibrilleren (n = 1) en acute pancreatitis / cholecystitis (n = 2). Alle andere patiënten hadden nonspecifieke niet acute ontslagdiagnoses. De gemiddelde ziekenhuiskosten per patiënt waren €1.580. De geschatte jaarlijkse acute zorgkosten in Nederland voor laag-risico pijn-op-de-borst patiënten bedragen €30.438.700.

Naast de vroege identificatie van laag-risico patiënten, kan een prehospitale risicobeoordeling ook een snelle identificatie van hoogrisico patiënten teweegbrengen. In **hoofdstuk 8** is onderzocht of patiënten met een hoog risico op vroege revascularisatie pre-hospitaal kunnen worden geïdentificeerd. Dit was een prospectieve cohortstudie onder 1289 opeenvolgende patiënten met verdenking op een NSTE-ACS, waarbij de HEART score inclusief point-of-care troponine werd uitgevoerd door ambulancemedewerkers. Het eindpunt was revascularisatie (PCI of CABG) binnen 30 dagen na opname. In totaal 164 patiënten (13%) werden binnen 30 dagen gerevasculariseerd. Van de 99 patiënten (8% van de totale groep) met een verhoogd point-of-care troponine ondergingen 49 (49%) revascularisatie. Van de 180 patiënten (14%) met een hoog-risico HEART score ondergingen 52 (29%) revascularisatie. Zowel een verhoogd troponine (OR 8.7) als hoog-risico HEART score (OR 3.6) waren significant geassocieerd met revascularisatie na univariate analyse. Na multivariate regressieanalyse bleef een verhoogd point-of-care troponine de sterkste voorspeller voor revascularisatie. Mogelijk profiteren patiënten met verhoogde point-of-care troponine van directe overdracht naar een PCI-centrum.

Tot nu toe was al het beschreven onderzoek observationeel. Prehospitale risicobeoordeling en troponineresultaten werden niet geïmplementeerd in prehospitale behandelbeslissingen. Omdat de eerdergenoemde studies de haalbaarheid van een prehospitale risicobeoordeling wel aantoonden, werd fase 3 van de Famous Triage-studie gestart. In **hoofdstuk 9** wordt de opzet van deze fase gerapporteerd. Het doel is om verder te beoordelen of pre-hospitaal HEART score management inclusief point-of-care troponinemeting en het vervolgens niet vervoeren van laag-risico patiënten naar het ziekenhuis haalbaar is en niet onderdoet voor het huidige prehospitale management.

TOEKOMSTPERSPECTIEVEN

Het belangrijkste onderwerp van dit proefschrift was de prehospitale risicobeoordeling bij patiënten met een mogelijk non-ST-elevatie acute coronair syndroom. De resultaten tonen aan dat deze aanpak haalbaar is en waarschijnlijk leidt tot aanzienlijke kostenbesparingen gezien de hoeveelheid diagnostiek die wordt uitgevoerd bij laag-risico patiënten. Hoewel deze bevindingen goede vooruitzichten bieden, hadden onze studies verschillende beperkingen, waaronder een beperkte sample size en een niet-gerandomiseerde opzet. Aanvullend onderzoek bij grotere patiëntgroepen en een gerandomiseerde opzet is wel nodig voordat prehospitale risicobeoordeling kan worden geïmplementeerd in ambulance- en eventueel huisartsrichtlijnen. Dit onderzoek is van groot maatschappelijk belang, gezien de hoge prevalentie van cardiovasculaire risicofactoren, waaronder diabetes en hypertensie wereldwijd, en vanwege de vergrijzing van de bevolking, waardoor wordt verwacht dat het aantal patiënten met vermoedelijke NSTE-ACS in de toekomst zal toenemen.

Patiënten met verdenking op NSTE-ACS vormen een grote en heterogene groep waarin snelle risicobeoordeling en daaropvolgende behandelbeslissingen cruciaal zijn. De uitdaging om het zorgproces bij die patiënten efficiënter te maken, wordt al tientallen jaren aangepakt en er is sindsdien al aanzienlijke vooruitgang geboekt, bijvoorbeeld door versnelde en verbeterde laboratoriumbepalingen, ontwikkeling van internationale protocollen en digitalisering van de gezondheidszorg. Bij verdenking op NSTE-ACS is zowel de identificatie van laag-risico patiënten als die van hoog-risico patiënten verbeterd doordat de doorlooptijd van laboratoria en de sensitiviteit van laboratoriumbepalingen aanzienlijk zijn verbeterd. De in- en exclusie van NSTE-ACS met behulp van beslisschema's op basis van troponinebepalingen zijn versneld van een protocol van 6 uur naar protocollen van 3 uur of zelfs van 1 uur. Echter, er zijn nog diverse manieren om de gezondheidszorg bij verdenking op NSTE-ACS te verbeteren.

Plaats en timing van risicobeoordeling bij verdenking op NSTE-ACS Risicobeoordeling bij verdenking op NSTE-ACS wordt tot nu toe uitgevoerd in het ziekenhuis. Gezien de resultaten die in dit proefschrift zijn gepresenteerd, is het de vraag of laag-risico patiënten daadwerkelijk naar het ziekenhuis moeten worden overgebracht. Om echter de non-inferioriteit van prehospitale risicobeoordeling ten opzichte van hospitale risicobeoordeling te bewijzen, is verder onderzoek noodzakelijk. Desalniettemin zijn er al verschillende verbeteringen mogelijk.

Zoals gezegd is (seriële) troponinebepaling een hoeksteen voor in- en exclusie van NSTE-ACS. Deze parameter duurt vaak het langst in het risicobeoordelingsproces. Tot nu toe worden patiënten eerst naar het ziekenhuis vervoerd en in een ziekenhuisbed geplaatst voordat bloed wordt afgenomen. Daarna wordt dit bloed verstuurd naar het ziekenhuislaboratorium en zijn de troponineresultaten ongeveer 45-60 minuten na ontvangst bekend. Om de tijd tot troponineresultaten te verkorten, kan er al bloed worden afgenomen in de ambulance. Als dit prehospitaal afgenomen bloed bij aankomst direct naar het laboratorium wordt gestuurd, kan dit ongeveer 30-45 minuten wachttijd besparen. Bovendien, als een tweede troponinemeting nodig is, kan dit aanzienlijk eerder worden uitgevoerd.

Daarnaast wordt ook een ECG in de ambulance gemaakt en deze is bij aankomst in het ziekenhuis beschikbaar voor de arts voor een eerste risicobeoordeling. Aangezien het ECG digitale informatie is, kan deze worden doorgestuurd naar het elektronische patiëntendossier van de patiënt, wat een eerdere risicobeoordeling in het ziekenhuis kan faciliteren.

Eerdere behandelbeslissingen Net als veel andere onderzoeken gaat dit proefschrift vooral over het risico op ziekte. Het primaire eindpunt van de HEART score is echter major adverse cardiac events (MACE). Dit eindpunt omvat zowel lichamelijke aandoeningen: acuut coronair syndroom en overlijden, als behandeling: revascularisatie. Het potentiële voordeel van prehospitale risicostratificatie wordt bepaald door vervoersbeslissingen door de ambulancemedewerker. De beslissende factor voor het wel of niet overplaatsen van een patiënt is voornamelijk de noodzaak tot (ziekenhuis) behandeling. Het is mogelijk om een laag-risico patiënt thuis te laten, omdat deze patiënt geen onmiddellijke diagnostiek of behandeling in het ziekenhuis nodig heeft. De identificatie van hoog-risico patiënten moet ook gebaseerd zijn op de noodzaak tot diagnostiek en behandeling. Tot dusver zijn risicoscores vaak gebaseerd op het risico op een hartinfarct of het risico op sterfte. Naast advies over observatietijd op de hartbewaking en advies over de timing van bijvoorbeeld coronairangiografie, volgen er geen concrete aanbevelingen. Daarom moeten toekomstige risicocalculatoren of klinische beslisregels meer gericht zijn op het

risico van een behandeling. Een patiënt met een hoog risico op sterfte heeft mogelijk geen baat bij directe overdracht naar een PCI-centrum, terwijl een patiënt met een hoog risico op revascularisatie dat wel heeft.

Toekomstige troponinebepaling Snelle diagnostiek is essentieel voor vroege behandelbeslissingen. Met de huidige point-of-care troponine apparaten wordt binnen 10-12 minuten de 'zogenoemde' verbeterde vierde generatie troponine gemeten. Omdat deze meting niet gevoelig genoeg is om troponinestijging kort na het begin van klachten te detecteren, blijft een tweede meting noodzakelijk. En zelfs dan zal de test niet zo sensitief zijn als de hoogsensitieve troponinebepalingen die tegenwoordig in het ziekenhuis worden gebruikt.

Vanwege de toegenomen sensitiviteit van laboratorium troponine zijn de klinische ACS in- en exclusie protocollen aanzienlijk versneld. Talrijke onderzoeken naar directe in- en exclusie zijn uitgevoerd en hebben aangetoond dat ACS bij patiënten met zeer lage of niet-detecteerbare niveaus van hoogsensitief troponine veilig kan worden uitgesloten. De huidige point-of-care troponinebepalingen zijn niet sensitief genoeg voor deze 0-uurbenadering en om tegemoet te komen aan de snel ontwikkelende klinische benadering zijn sensitievere point-of-care troponine-apparaten noodzakelijk. Omgekeerd is ook de rule-in benadering aanzienlijk versneld en lijken patiënten met verdenking op NST-ACS en een troponine > 52 ng/L op oh of delta troponine van ± 5 ng/L na 1h in aanmerking te komen voor vroege coronaire angiografie voor snelle detectie en revascularisatie van culprit laesies. Het huidige point-of-care troponine kan pre-hospitaal worden gebruikt voor deze rule-in benadering bij patiënten met een troponine ≥ 40 ng/L.

Vermeldenswaardig is nog dat alle diagnostische algoritmen altijd moeten worden gebruikt in combinatie met klinische beoordeling van vitale functies, risicofactoren, het ECG en klachten. Behandelingsbeslissingen op basis van alleen troponine moet ten allen tijde worden vermeden.

Transmurale zorg Voortbouwend op de transmurale zorg door samenwerking en gegevensuitwisseling tussen ambulance en ziekenhuis, zou er ook een essentiële rol kunnen zijn voor huisartsen. Naast de patiënten die per ambulance naar het ziekenhuis worden overgebracht, is er ook een groot aantal patiënten met thoracale klachten dat de huisarts bezoekt. Wanneer de klachten verdacht zijn voor NSTE-ACS, verwijzen huisartsen hun patiënten naar het ziekenhuis voor snelle risicostratificatie. Maar ook huisartsen kunnen een HEART score inclusief troponinebepaling uitvoeren. Op die manier kan de doorverwijzing van een aanzienlijk aantal patiënten mogelijk worden

voorkomen. Bovendien kunnen patiënten ook sneller naar het ziekenhuis worden verwezen indien er een vermoeden op NSTE-ACS is en het point-of-care troponine is verhoogd en/of het ECG toont verdachte afwijkingen. Voor een goede samenwerking tussen alle gezondheidswerkers binnen en buiten het ziekenhuis zijn gemakkelijke communicatiemethoden, snelle en veilige informatie-uitwisseling en 'transmurale' vergoeding essentieel.

Vergoeding van zorg Prehospitale risicostratificatie met daaropvolgende behandelbeslissingen kan leiden tot aanzienlijke kostenbesparingen, bijvoorbeeld door het vermijden van onnodig vervoer van laag-risico patiënten en door een mogelijk kortere ziekenhuisopname van hoog-risico patiënten. Dit kan een van de methoden zijn om verdere groei van de zorguitgaven te beperken. Er zijn echter diepgaandere kostenanalyses nodig naar onder andere kosten op lange termijn en het effect op huisartsbezoeken, verwijzingen en diagnostiek. Een van de knelpunten van de transmurale benadering in dit proefschrift is de huidige financieringsstructuur van de gezondheidszorg. Tot dusver wordt alleen ziekenhuiszorg die in het ziekenhuis wordt verricht vergoed door de zorgverzekering. Prehospitale risicobeoordeling wordt, met uitzondering van lokale (pilot) projecten, over het algemeen niet gefinancierd. Indien laag-risico patiënten in de toekomst niet naar het ziekenhuis worden overgebracht, zullen ziekenhuizen daadwerkelijk inkomsten verliezen als de huidige vergoedingsstructuur wordt gehandhaafd.

Het toekomstige ziekenhuis We verwachten dat het toekomstige ziekenhuis aanzienlijk zal verschillen van het ziekenhuis zoals we dat nu kennen. In de eerste plaats door demografische veranderingen van de hele samenleving, maar ook doordat de ziekenhuiszorg steeds meer gecentraliseerd wordt. Laag-risico patiënten worden prehospitaal geïdentificeerd en worden doorverwezen naar de eerstelijnszorg. Patiënten die bij de perifere ziekenhuizen binnenkomen, zullen ouder zijn, kwetsbaarder zijn en meer comorbiditeiten hebben. Ziekenhuisverblijf wordt zo snel mogelijk vervangen door poliklinische behandeling. Hoog-risico patiënten die gespecialiseerde interventies nodig hebben, worden gecentraliseerd in een beperkt aantal ziekenhuizen. Concluderend, de gehele gezondheidszorg zal in toenemende mate transmuraal worden en de ziekenhuismuren zullen figuurlijk vervagen. Dit proefschrift behandelt een belangrijke stap om de aanpak bij verdenking op NSTE-ACS aan te passen aan het toekomstige gezondheidszorgsysteem.

List of publications

LIST OF PUBLICATIONS

1. van Dongen DN, Ottervanger JP, Tolsma R, et al. In-Hospital Healthcare Utilization, Outcomes, and Costs in Pre-Hospital-Adjudicated Low-Risk Chest-Pain Patients. *Appl Health Econ Health Policy*. 2019;17(6):875-882. doi:10.1007/s40258-019-00502-6

2. van Dongen DN, Fokkert MJ, Tolsma RT, et al. Value of Prehospital Troponin Assessment in Suspected Non-ST-Elevation Acute Coronary Syndrome. *Am J Cardiol*. 2018;122(10):1610-1616. doi:10.1016/j.amjcard.2018.07.037

3. van Dongen DN, Tolsma RT, Fokkert MJ, et al. Pre-hospital risk assessment in suspected non-ST-elevation acute coronary syndrome: A prospective observational study. *Eur Heart J Acute Cardiovasc Care*. 2020;9(1_suppl):5-12. doi:10.1177/2048872618813846

4. van Dongen DN, Fokkert MJ, Tolsma RT, et al. Accuracy of pre-hospital HEART score risk classification using point of care versus high sensitive troponin in suspected NSTE-ACS [published online ahead of print, 2019 Oct 8]. *Am J Emerg Med*. 2019;S0735-6757(19)30597-2. doi:10.1016/j.ajem.2019.158448

5. van Dongen DN, Badings EA, Fokkert MJ, et al. Pre-hospital versus hospital acquired HEART score for risk classification of suspected non ST-elevation acute coronary syndrome [published online ahead of print, 2020 Jun 15]. *Eur J Cardiovasc Nurs*. 2020;1474515120927867. doi:10.1177/1474515120927867

6. van Dongen DN, Tolsma RT, Fokkert MJ, et al. Referral decisions based on a prehospital HEART score in suspected non-ST-elevation acute coronary syndrome: design of the FamouS Triage 3 study [published online ahead of print, 2020 Jun 18]. *Future Cardiol*. 2020;10.2217/fca-2019-0030. doi:10.2217/fca-2019-0030

Dankwoord

Wat is het een bijzonder en ook wel vreemd gevoel om dit dankwoord te schrijven. Enerzijds voelt het alsof de tijd voorbij is gevlogen, anderzijds heeft het soms gevoeld alsof het doel om te promoveren een grap was die ik nooit serieus had moeten nemen.

Op donderdag 1 januari 2015 begon ik, als 'versgebakken' dokter, mijn avontuur als arts-assistent cardiologie in het Deventer ziekenhuis met als doel om een half jaar later goed beslagen ten ijs te komen in 'het Isala' en dan een opleidingsplek tot cardioloog te bemachtigen. Ik heb in Deventer een fantastische eerste tijd gehad en enorm veel geleerd waardoor ik in Isala inderdaad een goede start kon maken. Het duurde dan ook niet lang voordat ik op gesprek mocht komen bij dr. Ramdat Misier, de opleider aldaar.

Het gesprek begon goed; goede indruk, kennis op niveau, enthousiast, maar daarna ging het de verkeerde kant op; nog wel jong, weinig ervaring, geen enkele publicatie. Gelukkig had hij wel een goede oplossing; ik was uitermate geschikt voor een researchplek bij dr. van 't Hof, die zocht nog iemand. Wát?! Researchplek? Dat betekent toch zoiets als 4 jaar verstoffen achter een laptop bakkeleiend over een molecuul dat wellicht invloed heeft op hart- en vaatziekten? Daar ging mijn plan om zo snel mogelijk in opleiding te komen.

Ik ging op gesprek bij dr. van 't Hof. Best aardig eigenlijk, die man, en na decennia van onderzoek doen nog ontzettend enthousiast. Klonk toch wel goed, dat Famous onderzoek. Wel een beetje een patserige naam. Ook best zinnig, maatschappelijk relevant, en eigenlijk ook niet stoffig. Het was misschien toch wel een mooie kans, zo'n promotieplek. Na een periode van nadenken en sparren met naasten besloot ik de uitdaging aan te gaan.

En wat ben ik blij dat ik dat gedaan heb! Ik had dit leerproces voor geen goud willen missen. Onderzoek doen is een enorm understatement voor wat ik allemaal heb geleerd en gedaan de afgelopen 4 jaar. Natuurlijk zijn wetenschappelijk leren schrijven en statistiek een belangrijk onderdeel, maar er waren veel meer uitdagingen. Zo is onderzoek niet mogelijk zonder financiën, doe je onderzoek niet alleen maar met een team en is het daarbij ook belangrijk dat alle neuzen dezelfde kant op staan. Als er veel potentie in onderzoek zit, dan zijn er altijd anderen die dat ook zien en als je een, naar eigen mening, prachtig artikel hebt geschreven kan het toch een uitdaging zijn om een blad te vinden dat het wil publiceren. Maar boven alles heb ik geleerd dat werkplezier en een fijn thuis de grootste voorwaarden zijn om deze marathon uit te rennen!

DANKWOORD

Geachte **prof. dr. van 't Hof, beste Arnoud**, promoveren stond niet op mijn planning toen ik in Isala aan de slag ging. Maar toen je mij vertelde over Famous Triage kon ik niet anders dan enthousiast worden over dit onderzoek, zo praktisch, doelmatig en revolutionair. Dankjewel voor het overbrengen van je inspirerende enthousiasme en creatieve denken wat, juist in de wetenschap, heel goed mogelijk is! Helaas verliet je Zwolle, iets wat ik nog altijd jammer vind, maar gelukkig zijn we elkaar niet helemaal uit het oog verloren en ik ben vereerd dat je nu mijn promotor bent.

Geachte **dr. Ottervanger, beste Jan Paul**, Ik kwam op jouw pad (werd je in de maag gesplitst) nadat Arnoud professor werd in Maastricht. En dat was best wennen. Voor ons allebei. Inmiddels ben je dan wel niet mijn vader, maar fungeer je soms wel in die rol. Mijn doel was om nooit te huilen, want jij zei dat alle meisjes wel een keer huilen en de jongens nooit. Helaas is het me (één keertje) niet gelukt. Maar dat gaf niet en ik heb er geen spijt van gehad. Het was goed om een mentor te hebben die mij er soms aan herinnerde dat promoveren geen sprint maar een marathon is, dat werk uiteindelijk nooit het belangrijkste is, dat moeder worden het mooiste is wat er is, dat je altijd eerst tot 10 moet tellen en dat je altijd de grote lijn voor ogen moet houden. Dankjewel voor de goede gesprekken en dat ik je ook op persoonlijk vlak heb mogen leren kennen. Dankjewel voor de begeleiding bij ons onderzoek, zonder jou was dit boekje er niet geweest.

Geachte **dr. Slingerland, beste Robbert,** een belangrijk aspect van ons onderzoek was de prehospitale troponinebepaling. Betrokkenheid van het klinisch chemisch laboratorium was dan ook onmisbaar en hoewel de bemanning van de cardiologie nog weleens veranderde, stond jij aan de voet van het Famous Triage onderzoek. Value based healthcare staat bij jou hoog in het vaandel. Dankjewel voor je betrokkenheid en de deur die altijd open stond op V1.2. Wellicht ontmoeten we elkaar opnieuw bij een volgend mooi project!

Geachte promotiecommissie, **prof. dr. J.W.L. Cals, prof. dr. O. Bekers, prof. dr. H.J.G.M. Crijns, prof. dr. J.P.S. Henriques, dr. J. Meeder.** Mijn dank voor jullie tijd en aandacht bij de beoordeling en verdediging van het manuscript.

Inmiddels ben ik alweer 5 jaar werkzaam in Isala en heb ik ontzettend veel mensen leren kennen die ik het liefst allemaal persoonlijk zou willen bedanken voor hun directe of indirecte bijdrage aan dit boekje. Zo werd het polileven (meestal) een stuk makkelijker gemaakt door alle medewerksters in de frontoffice en kon ik met menig vraag terecht in

de backoffice, waar ook altijd zo'n fijne dropjespot staat. De planners **Willemien, Windy** en **Jennita** zorgden ervoor dat de kliniek op rolletjes liep en **Frank** liet geen brief met typefout de deur uit gaan.

Ik wil alle cardiologen in het hartcentrum te Isala bedanken voor de opleiding die in de Zwolse periferie gevestigd is. Mijn specifieke dank voor mijn opleider, **Anand Ramdat Misier** en vice-opleider **Jorik Timmer** voor het gestelde vertrouwen en de begeleiding van de opleiding. **Ahmet Adiyaman** door wie elektrofysiologie soms zelfs bijna simpel lijkt, **Irlando Andrade Ferreira** de 'held' van de CCU, **Balazs Berta** onze stille kracht op de HCK, de swingende pianist **Jan-Henk Dambrink**, onze carnavalsvierder en device goeroe **Peter Paul Delnoy**, de wijze **Arif Elvan**, **Hans Geertman** waardoor ontslagbrieven weer leesbaar werden, **Georges Gerritsen**, **Abdul Ghani** bij wie onderwijs hoog in het vaandel staat, **Marcel Gosselink** mede dankzij jou hebben we met CRM mooie resultaten geboekt, **Veemal Hemradj** altijd bereid iets uit te leggen, de altijd energieke **Rik Hermanides**, **Pieter Hoogslag**, **Jana Hrudova**, **Jasveen Kandhai**, **Sinem Kilic**, **Ed de Kluiver** die mij heeft leren skien, **Maarten van Leeuwen** onze nieuwe interventiespecialist, **Miguel Lemmert**, **Balazs Manfai** 'een panter leest niet', **Tom Meijers** de STEMI's komen het liefst wanneer jij dienst hebt, **Mohamed Mouden** (MoMo!) ik draag je een warm hart toe, **Anton Mulder**, **Erik Oosterwerff** voor goede gesprekken, **Dennis Rooker** bron van levendige humor in de echoput, **Vincent Roolvink** met de hoogste pijngrens ter wereld, swingende kerstdrummer **Jaap Jan Smit** met zijn aanstekelijke lach, **Rik Steenmeijer** hoogste ESC examenscore aller tijden!, **Karen Thomas**, de sportieve **Marleen Veldhorst**, kersverse cardioloog **Joshua Verbakel**, **Maureen van der Vlugt** van wie ik echocardiografie leerde beoordelen, onze levensgenieter **Olivier Witte**, voor goede gesprekken, veel lol en relativeringslessen, **Shu Yokota** onze eigen Yiruma.

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De 7 sloten worden nog altijd bewandeld: werk, promotie, baby, huis, vrijwilligerswerk, hobby's, vrienden, en nog altijd staan jullie voor mij klaar. Dank jullie wel voor jullie niet aflatende steun, jullie bemoediging, bevestiging en vertrouwen. Ik voel mij enorm bevoorrecht met de jeugd en opleiding die ik dankzij jullie heb gehad.

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"Leg uw werk in de handen van de Here,
dan zullen uw plannen werkelijkheid worden."

Spreuken 16:3

Curriculum Vitae

CURRICULUM VITAE

Dominique van Dongen was born on May 17th 1989 in Ermelo, the Netherlands. After graduating from high school in 2007 (Christelijk College Groevenbeek, Ermelo) she studied Biomedical Sciences for a year before attending medical school at the Vrije Universiteit van Amsterdam. From 2011 onwards, Dominique carried out her clinical internships at various hospitals. In the final year Dominique executed her Master Thesis at the cardiology department of the Deventer hospital. This research project triggered her interest in cardiology. After successfully completing the research project, Dominique graduated in 2014 with ECTS grade A.

After obtaining her MD, she started her career as a medical doctor at the Department of Cardiology in Deventer and went to the Department of Cardiology in Zwolle 10 months later. In 2016 she acquired a research placement and started with medical research which led to the current thesis. In 2018 she simultaneously commenced her training as cardiologist in Zwolle. Currently, Dominique is in the second year of her residency, working at the Department of Internal medicine in Deventer Hospital. She aims to register as a cardiologist in 2025. Her fields of interest are interventional cardiology and healthcare improvement. Apart from her PhD and work as clinical doctor, Dominique is committed as a fundraising manager to foundation iSTEPup, which aids adolescents with insufficient financial means in low- and middle-income countries to become professional healthcare providers in their countries. She is an aspiring piano player and enjoys painting, skiing and gardening. She is married with her great love Ruben with whom she has a daughter Juliëtte. Together they will soon welcome a second daughter.