Prehospital triage and risk assessment in STEMI patients

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Foar myn heit en mem, Iwan en Sven

CONTENTS

ABBREVIATIONS

ACC	American College of Cardiology
ACS	acute coronary syndrome
AHA	American Heart Association
BI	balloon inflation
BMS	bare metal stent
CABG	coronary artery bypass grafting
CK	creatin kinase
CKMB	Creatin Kinase-MB
CVA	cerebrovascular accident
CX	circumflex artery
D2B	door-to-balloon
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DIDO	door-in-door-out
DM	diabetes mellitus
ECG	electrocardiogram
EMS	emergency medical services
ER	emergency room
ESC	European Society of Cardiology
FMC	first medical contact
G2I	grade 2 ischemia
G3I	grade 3 ischemia
GP	glycoprotein
GPI	GPIIb/IIIa inhibitor
HD	high dose
IRV	infarct related vessel
LAD	left anterior descending
LBBB	left bundle branch block
MACE	major adverse cardiac events
MBG	myocardial blush grade
MI	myocardial infarction
Min	minutes
OHCA	out of hospital cardiac arrest
On-TIME	Ongoing Tirofiban in Myocardial Infarction
IQR	interquartile range
pPCI	primary percutaneous coronary intervention
PCI	percutaneous coronary intervention
PHT	prehospital triage
RCA	right coronary artery
SD	standard deviation
SO	symptom onset
STEMI	ST-elevation myocardial infarction
STR	ST-segment resolution
TIMI	thrombolysis in myocardial infarction
TVR	target vessel revascularization
UFH	unfractioned heparin
uTVR	urgent target vessel revascularization
VD	vessel disease

CHAPTER 1

INTRODUCTION
PREHOSPITAL DIAGNOSIS, TRIAGE AND TREATMENT IN PATIENTS WITH ST ELEVATION MYOCARDIAL INFARCTION

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INTRODUCTION

The treatment of acute ST elevation myocardial infarction (STEMI) has greatly improved in the last three decades, especially after the introduction of primary percutaneous coronary intervention (PCI). However, primary PCI is available in selected centres only, thus necessitating transportation of the STEMI patient. Improvement in the logistics of care for these patients is associated with significant improvement of patient outcome. Both the American Heart Association (AHA) and the European Society of Cardiology (ESC) STEMI guidelines recommend pre-hospital infarct diagnosis as a class I recommendation [w1-w2]. Despite this, the large majority of STEMI patients are only diagnosed after arrival in the hospital [1]. Therefore, great care should be taken in the initial diagnosis, risk assessment and triage, subsequent transfer and the distance of transportation as well as pre- and in-hospital time delays in these patients.

PRE-HOSPITAL INFARCT DIAGNOSIS AND TYPE OF TRANSFER

STEMI patients can be diagnosed in the pre-hospital phase in two ways. The first option is diagnosis in the ambulance via an emergency medical services (EMS) call (118 or 911) by the patient or by a general practitioner. The second option is diagnosis at a referral non-PCI centre after self-referral of the patient or when no pre-hospital electrocardiogram (ECG) is performed by EMS in the ambulance. Pre-hospital diagnosis in the ambulance gives the best outcomes for STEMI patients, since pre-hospital treatment can be started directly in the ambulance after diagnosis and triage [2-3]. Subsequently, these patients are directly transferred in an ambulance from the pick-up place to the nearest PCI centre with 24/7 service, bypassing the emergency departments of the nearby referral non-PCI centres. The second option, diagnosis at a non-PCI centre, also occurs often, especially in rural areas. These patients are transported to a PCI centre, following diagnosis and triage of STEMI, preferably at the emergency department. STEMI patients can also be diagnosed in the PCI centre after self-referral, however, no pre-hospital triage, diagnosis and treatment is performed in these patients (Figure 1). Whether telemedicine can further improve pre-hospital diagnosis in STEMI remains to be evaluated. A previous study showed a slightly higher incidence of false positive infarct diagnoses with ambulance or field triage (5% vs. 1%), which can be overcome by electronic transfer of the ECG to the PCI centre. However, this is often associated with extra time delay [4].

ORGANISATION OF NETWORKS

Since the angiographic and clinical outcome of STEMI patients is dependent on the type of pre-hospital diagnosis and type of transfer, more effort should be applied in improving the organisational issues in the pre-hospital phase. First of all, every region should be organised according to local practice, since there is no ‘one size fits all’ solution. The policymakers/(local) government play a pivotal role in order to optimise the system, that is, to ban the restriction that EMS is only used for inter-hospital transfer, or that ambulances are

not allowed to bypass non-PCI centres. Second, it is important to make patients and general practitioners aware of the fact that pre-hospital diagnosis with ambulance transport has better outcomes for STEMI patients than referring via a referral non-PCI centre, referring via general practitioners or self-referring. Third, use of pre-hospital ECG equipment with a computerised algorithm or electronic transmission of an ECG to a PCI centre can be helpful to achieve a faster initial diagnosis, and suggests a trend for a lower risk of mortality [1]. Fourth, diagnosis of STEMI can be performed by highly trained paramedics using ECG equipment with a computerised algorithm or teletransmission of the ECG.

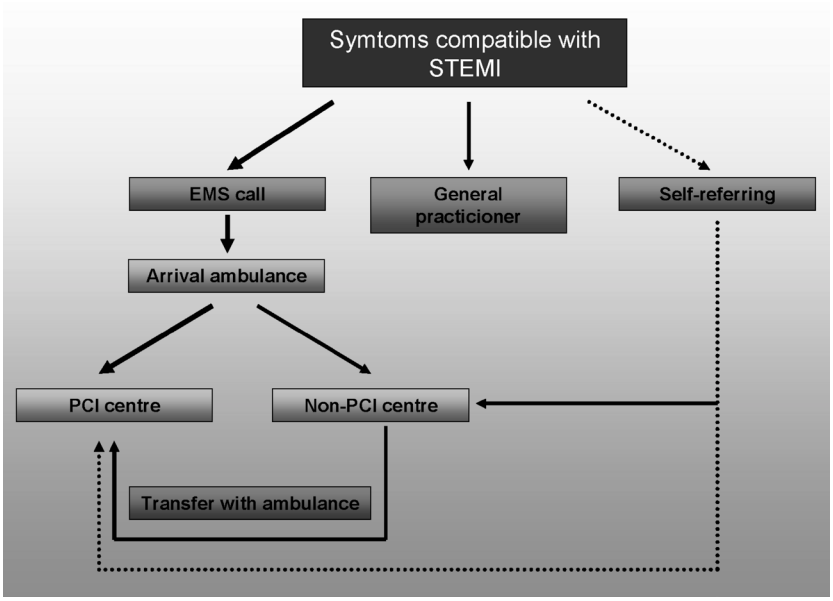

Figure 1. Pre-hospital management of ST elevation myocardial infarction (STEMI) patients.
EMS, emergency medical services; PCI, percutaneous coronary intervention.
Thick black lines: preferred pathway; black narrow lines; to be avoided.

PRE-HOSPITAL RISK ASSESSMENT AND TRIAGE

Early risk stratification is important to classify a patient's risk (low, intermediate and high), and to identify which STEMI patients benefit from early interventions, that is, patients who present early benefit the most from reperfusion therapy. Conversely, patients who present late are at lower risk, have already survived the pre-hospital phase and benefit less from reperfusion therapy [5, w3]. It was demonstrated that high-risk patients benefit the most from short door-to-balloon (D2B) times [w4].

Several risk scores have been developed to classify a STEMI patient's ischaemic risk, of which the TIMI risk score and the GRACE risk score are the most known and adopted ones [w5-w6]. However, these risk models are bedside scores used in-hospital to predict mortality. Morrow et al have developed a simple risk index based on age, heart rate and systolic blood pressure for predicting 30-day mortality [6]. This is the only risk score known for STEMI patients which can be used in the pre-hospital phase. Additionally, it is known that older age, higher Killip

class, anterior infarction, elevated heart rate, lower systolic blood pressure, or new left bundle branch block play a pivotal role in the judgement of a patients's risk in the pre-hospital phase. Besides these indicators, recently, the predicting value on clinical outcome of specific markers in the pre-hospital phase, like the extent of ST segment deviation, grade of ischaemia and QRS width, are of great interest in STEMI patients.

TIME DELAYS

Time is very important in the treatment of STEMI patients [7]. The time from symptom onset (SO) until balloon inflation (BI), defined as ischaemic time, is crucial for patient outcome. Since the time from SO until first medical contact (FMC), the so-called 'patient delay', is hampered by recall and information bias and confounding, recently more attention has been paid to the new phrase 'systemdelay' (FMC-reperfusion therapy) and its derivates (Figure 2).

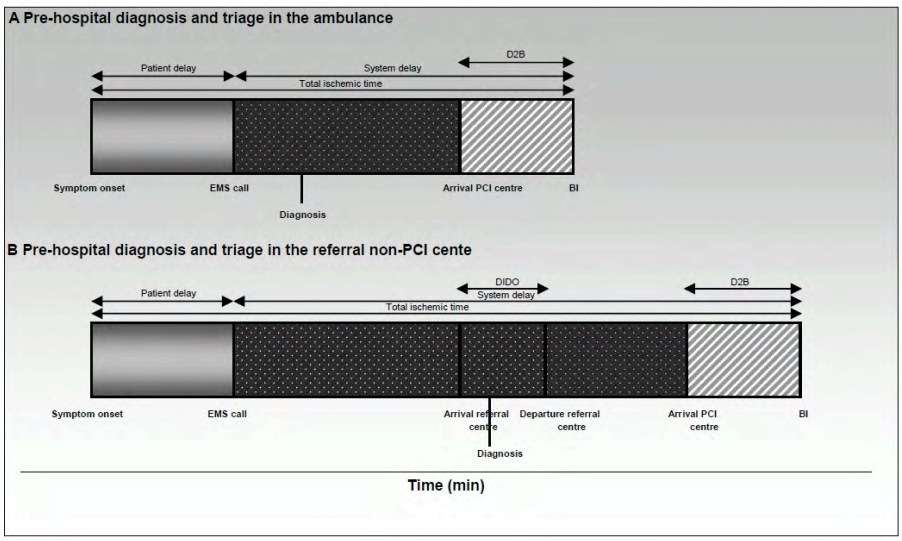

Figure 2. The different time delays are demonstrated for ST elevation myocardial infarction (STEMI) patients for patients treated with pre-hospital diagnosis and triage in the ambulance (A) and treated with pre-hospital diagnosis and triage in the referral non-percutaneous coronary intervention (PCI) centre (B).
BI, balloon inflation; DIDO, door-in-door-out time; D2B, door-to-balloon time; EMS, emergency medical services; min: minutes.

A longer 'system-delay' is associated with a higher mortality [8] Furthermore, several studies have focused on decreasing the D2B time. A shorter D2B time is associated with improved outcome [9-10]. Since not all STEMI patients are directly transferred to a PCI centre, but are first transported to a non-PCI centre, the door-in-door-out (DIDO) time has recently been described as a clinical performance measurement. A shorter DIDO time is associated with shorter reperfusion delays and lower in-hospital mortality [w7]. Previous studies showed that optimising logistics by pre-hospital diagnosis and triage in the ambulance can help to reduce

treatment delays and improve outcomes [3, 11, 12, w8-w12]. Especially at longer distance from the patient's residence to the PCI centre, pre-hospital diagnosis and triage in the ambulance was associated with a shorter time to treatment, and a more favourable outcome, compared with referral via a non-PCI referral centre [2].

PRE-HOSPITAL TREATMENT STRATEGIES

The pre-hospital treatment for STEMI patients has been improved during the last decade. Pre-hospital thrombolytic therapy and new antiplatelet and antithrombotic agents were developed (Table 1).

Table 1. Overview of medical treatment strategies for STEMI patients in the pre-hospital phase versus the in-hospital phase

Agents with proven efficacy in the pre-hospital phase	*Study and/or authors*	*Study design*
Thrombolytic therapy	- The European Myocardial Infarction Project Group	- Multicentre, double blind trial
	- Bjorklund et al.	- Prospective cohort study
High dose heparin	HEAP trial, Liem et al.	Single centre, open-label trial
Aspirin and heparin	Zijlstra F et al.	Cohort study
Aspirin, heparin/enoxaparin and clopidogrel	CIPAMI trial, Zeymer U et al.	Multi-centre, randomized, open trial.
Aspirin, heparin, clopidogrel and tirofiban	On-TIME trial, Van 't Hof et al.	Multi-centre, randomized, double blind, placebo controlled clinical trial
Aspirin, heparin, clopidogrel and abciximab	EGYPT-ALT, De Luca et al.	Meta-analysis
Future		
Aspirin, heparin and ticagrelor	Atlantic trial	Multi-centre, randomized, parallel-group, double blind, placebo controlled clinical trial
Aspirin, P2Y12 blocker and bivalirudin	Euromax trial	Multi-centre, randomized, open-label clinical trial

Pre-hospital thrombolytic therapy

The introduction of thrombolytic therapy was a major improvement in the treatment of STEMI patients. Pre-hospital treatment with thrombolytic therapy reduced time to treatment by 1 h, and mortality by 17% compared with in-hospital thrombolytic therapy [13]. In a more recent analysis, it was shown that pre-hospital diagnosis and thrombolysis with trained paramedic personnel in the ambulance was associated with a shorter time to treatment, and a 30% reduced relative mortality risk compared with in-hospital thrombolysis [14]. In a randomised trial, Bonnefoy et al compared pre-hospital thrombolysis with primary PCI and found no difference in mortality or re-infarction [w13]. However, in the subgroup of patients who were treated within 2 h after SO, pre-hospital thrombolytic therapy reduced long term mortality [15]. Since multiple reports demonstrated a superior effect of primary PCI compared with

thrombolytic therapy, the latter therapy is only recommended in STEMI patients if the time from first medical contact balloon inflation time (FMC-BI) is more than 120 min (ESC) or more than 90 min (AHA) [w1-w2].

Antiplatelet and antithrombotic agents

Effective platelet inhibition is a cornerstone in the therapy of STEMI patients. The pre-hospital treatment effect of aspirin has not been studied individually. The only performed study investigating the effect of aspirin in STEMI patients was the ISIS-2 trial; however, this trial was not performed pre- versus in-hospital [w14]. The pre-hospital treatment effect of both aspirin and heparin was studied years ago and has been proven to be effective [16-17]. Upstream treatment with glycoprotein (Gp) IIb/IIIa inhibitors are administered pre-hospitally to STEMI patients. Pre-hospital versus in-hospital administration of tirofiban improved TIMI 2-3 flow pre-PCI and myocardial reperfusion in STEMI patients [18]. In the On-TIME 2 trial, early tirofiban administration was associated with improved pre and post-procedural reperfusion and improved clinical outcome as well [19]. Especially when administered in the golden hour, a concept adopted from thrombolytic studies, the effect of triple antiplatelet pretreatment, including tirofiban, was most effective [20]. In the On-TIME 2 trial, pre-hospital initiation of high-dose tirofiban significantly increased the number of patients with an aborted myocardial infarction, especially in patients with <70 min of symptoms. Studies performed with upstream administration of abciximab have shown comparable results [21]. Despite this evidence, the most recent guideline on myocardial revascularisation states that upstream treatment with Gp IIb/IIIa inhibitors is not recommended (class III recommendation). This recommendation is based on the negative results of abciximab facilitated PCI in the FINESSE trial [w15]. There is still no consensus about the pre-hospital versus in-hospital treatment effect of clopidogrel in addition to aspirin and heparin on outcome. The only randomised trial performed by Zeymer et al was stopped prematurely [22]. Newer antiplatelet agents like ticagrelor and prasugrel are nowadays also administered pre-hospitally to STEMI patients instead of clopidogrel; however, the effect of these agents needs to be further evaluated since the trials performed did not investigate the pre-treatment versus in-hospital treatment effect. A dedicated trial evaluating the effect of in-ambulance ticagrelor is currently running. Effects of direct thrombin inhibitors are also of great interest these days. Therefore, currently, a randomised trial to evaluate the effect of bivalirudin is performed. Overall, more research is needed to assess the efficacy of pre-treatment versus in-hospital treatment of the new antiplatelet and antithrombotic agents. In the near future, the pharmacological agents will probably be more tailored to the patient, considering the interindividual variability in response to antiplatelet and antithrombotic agents, and the patient's risk of bleeding.

CONCLUSION

A wide variety of therapeutic options are available for the pre-hospital care of STEMI patients. Optimisation of the care can be achieved by better logistics, risk assessment and triage. In

addition, early diagnosed STEMI in the ambulance is the ideal environment for initiating effective antiplatelet and/or antithrombotic treatment early after the onset of symptoms. This treatment might become further tailored to the individual patient in the future.

OUTLINE OF THE THESIS

This thesis addresses two important issues. **PART I** of the thesis focuses on the pre-hospital diagnosis and triage in the ambulance (field triage) and pre-hospital treatment of STEMI patients. In **PART II** electrocardiographic parameters of the diagnostic ECG of STEMI patients at risk were investigated.

The aim of **PART I** of the thesis was to determine how field triage and pre-hospital treatment of STEMI patients can be improved leading to better angiographic and clinical outcome for these patients.

Chapter 2 and 3 concern the relation between referral of STEMI patients via field triage versus referral via non-PCI centre by means of a cohort study (chapter 2) and a systematic review (chapter 3) with outcome. Chapter 4 demonstrates the influence of residential distance from a PCI centre on ischemic time in STEMI patients. In chapter 5 the relation between system delay and mortality for patients with an anterior versus non-anterior STEMI was investigated. Chapter 6 addresses whether early ambulance initiation of high dose clopidogrel in STEMI patients improves angiographic and clinical outcome compared to cathlab initiation.

The aim of **PART II** of the thesis was to determine which parameters of the diagnostic ECG are predictors for STEMI patients at high risk in the acute phase.

Chapter 7 addresses which baseline characteristics of STEMI patients are predictors for grade 3 ischemia (G3I) and the effect of G3I on outcome was investigated. Chapter 8 concerns the predictive value of initial ST-segment deviation in STEMI patients compared to ST-segment elevation.

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PART I PREHOSPTIAL DIAGNOSIS AND TRAGE OF STEMI PATIENTS

CHAPTER 2

PREHOSPITAL TRIAGE IN THE AMBULANCE REDUCES INFARCT SIZE AND IMPROVES CLINICAL OUTCOME

PREHOSPITAL TRIAGE

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ABSTRACT

BACKGROUND

We evaluated the effect of pre-hospital triage (PHT) in the ambulance on infarct size and clinical outcome and studied its relationship to the distance of patient's residence to the nearest percutaneous coronary intervention (PCI) centre.

METHODS

All consecutive ST-segment elevation myocardial infarction (STEMI) patients who were transported to the Isala klinieken from 1998 until 2008 were registered in a dedicated database. Of these, 2288 (45%) were referred via a spoke centre and 2840 (55%) via PHT.

RESULTS

PHT patients were more often treated within three hours after symptom onset (46.2% vs. 26.8%, $p<0.001$), more often had a post procedural TIMI 3 flow (93.0% vs. 89.7%, $p<0.001$), had a smaller infarct size (peak CK: 2188 ± 2187 vs. 2575 ± 2259 IU/l, $p<0.001$) and had a lower one-year mortality (4.9% vs. 7.0%, $p=0.002$). After multivariate analysis, PHT was independently associated with ischemic time less than three hours (OR: 2.45, 95% CI 2.13 to 2.83), a peak CK less than the median value (OR: 1.19, 95% CI 1.04 to 1.36) and a lower one-year mortality (OR:0.67, 95% CI 0.50 to 0.91). The observed differences between PHT patients and the spoke group were more pronounced in the subgroup of patients living >38 km from the PCI centre.

CONCLUSION

PHT in the ambulance is associated with a shorter time to treatment, a smaller infarct size and a more favourable clinical outcome, especially with longer distance from the patient's residence to the nearest PCI centre. Therefore, PHT in the ambulance may reduce the negative effect of living at a longer distance from the PCI centre.

INTRODUCTION

It is well known that rapid restoration of coronary blood flow in patients with ST-segment elevated myocardial infarction (STEMI) is crucial [1] to limit myocardial damage [2-3]. There are two established therapeutic strategies to achieve this: fibrinolysis and primary Percutaneous Coronary Intervention (pPCI), of which the latter is considered more effective [2, 4-7]. However, there is still debate about the time interval during which pPCI can be recommended. According to the American Heart Association/American College of Cardiology (AHA/ACC) pPCI is preferred if the delay between first medical contact and pPCI does not exceed 90 minutes (min) [8] and according to the European Society of Cardiology (ESC) this delay should not exceed 120 minutes (min) [9]. If the anticipated delay exceeds 90 min (AHA/ACC) or 120 min (ESC), fibrinolytic therapy may be an alternative, since it can be administered with a shorter delay in the ambulance or in a nearby spoke centre [10-11].

One of the possibilities to shorten delays and maximise the number of patients eligible for pPCI, is to transport STEMI patients directly to a PCI centre after pre-hospital triage (PHT) in the ambulance. Several studies have shown that this strategy can significantly reduce ischemic times compared to patients being referred via a spoke centre [12-15]. Recently, Pedersen et al. have demonstrated that PHT also improves outcome [15]. However, a recent analysis from the HORIZONS AMI study did not show a benefit for patients immediately transported to a PCI centre [16]. In addition, it is less well known if PHT is beneficial for patients living at a greater distance from a PCI centre. Therefore, we addressed both the question on efficacy and on distance in a large cohort of non-selected STEMI patients, who were directed to our centre either via a referral centre (spoke) or via PHT.

METHODS

Population

Since the early nineties STEMI patients referred to the Isala Klinieken were treated by pPCI. To improve the logistics of STEMI patients, the PHT project was initiated. This has gradually been implemented in the region, starting in 1998. At that time thirteen spoke centres referred their STEMI patients to our PCI centre, however this number decreased to eight spoke centres since new PCI centres opened. During the project all consecutive STEMI patients who were transported to our PCI-centre from 1998 until 2008 and underwent pPCI, were prospectively registered in a dedicated database. Criteria for the diagnosis of STEMI were: (1) history of cardiac symptoms of at least 10 min in the last 24 hours prior to presentation at the spoke or PCI centre, (2) elevated levels of Creatin Kinase (CK) or Creatin Kinase-MB (CKMB) and (3) concurrent electrocardiogram (ECG) changes: ST-segment elevation of >1mV in at least two adjacent electrocardiogram leads [17]. Information whether patients were transferred via referral centres (spoke group) in the network or via PHT (PHT group) was recorded. In addition information on infarct size, angiographic outcome and short and long term clinical outcome were registered as well. Infarct size was calculated as the peak level of CK (peak CK) within 48 hours after admission [18].

The distance via motorway to the nearest PCI centre was computerized using the postal codes of the patient's residence and the PCI centre. Subsequently the percentiles (25-75) of the computed distances were calculated. The PHT and spoke group were subdivided in short (≤38 km) and long distance (>38 km) based on the median distance from patient's residence to the PCI centre.

Patients were excluded if they did not have a confirmed diagnosis of acute myocardial infarction (CK <200 and no evidence of unstable plaque or culprit lesion at coronary angiography), the distance from patient's residence to the PCI centre was not available or if the distance from patient's residence to the PCI centre was ≥120 km (outer bound of referring area).

Triage for pPCI

PHT:

The algorithm of PHT has been described previously [19]. In brief: After patients dialed the emergency number, patients were triaged in the ambulance, if the ambulance was equipped with the PHT equipment. If STEMI was suspected, an ECG was made by highly trained paramedics and the computerised algorithm revealed an outcome. If a diagnosis of STEMI was made, the ambulance went straight to the catheterization laboratory of PCI centre, bypassing the emergency departments of the spoke centre.

Spoke:

If the ambulance was not equipped with the PHT equipment, the ambulance went to the nearest spoke centre where diagnosis and triage was performed. For diagnosis, an ECG was made immediately upon arrival. In case of a STEMI diagnosis, patients were transported to the catheterization laboratory of the PCI centre as soon as possible.

Walk-ins at the PCI centre were excluded since they did not receive pre-hospital triage.

pPCI procedure

In both situations (PHT and Spoke), the staff of the catheterization laboratory of the PCI-centre was pre-informed about the estimated time of arrival of the patient and was activated well before the arrival of the patient. In case the staff lived more than 30 min away from the PCI centre, they had to stay in the PCI centre when being on-call. Patients were pre-treated with an intravenous bolus of 5000 IU unfractionated heparin, 500 mg aspirin intravenously and subsequently with 600 mg clopidogrel and/or tirofiban (25 µg/kg bolus, 0.15 µg/kg/min maintenance infusion). PHT patients were pre-treated in the ambulance and spoke patients were pre-treated at the spoke centre and/or in the ambulance which transferred the patient form the spoke centre to the PCI centre.

Time intervals

Six different time intervals were evaluated:1.Time from symptom onset (SO) to infarct diagnosis (time diagnostic ECG) either in the ambulance or at a spoke centre (SO-Diagnosis) 2.Time from diagnosis till arrival at the PCI centre (Diagnosis-Door PCI) 3.Time from diagnosis to balloon inflation (BI) (Diagnosis-BI) 4.Time from arrival spoke centre to arrival PCI centre (Door-to-door:D2D) 5.Time from arrival at the PCI centre to BI for PHT patients and time from arrival spoke hospital to BI for spoke patients (Door-to-balloon: D2B) and 6.Total ischemic time defined as the time from SO to BI.

Statistical analysis

Statistical analysis was performed with SPSS 17.0. Continuous data were expressed as mean ± SD or median and interquartile range. Categorical data were presented as percentage. ANOVA was used for continuous data and Pearson's Chi-square test was used for the categorical data, respectively. We tested the associations between the variable 'PHT' and other baseline characteristics using univariate logistic regression. The Mann-Whitney test has been used to calculate the time intervals between the PHT group and the spoke group, since they were non-Gaussian distributed. To assess independent predictors of PHT, multivariate analysis was performed using a logistic regression analysis. In this analysis, univariate variables with a *p*-value <0.10 were included. In all the statistical analyses *p*-values ≤0.05 were considered as statistical significant.

The study was conducted according to the principles of the Declaration of Helsinki and the protocol was approved by the local institutional review board. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

Ambulance triage versus referral by spoke centre

From 1998, the first year of implementation of PHT in the ambulance, until 2008 5674 patients were referred to our institution with the intention to perform pPCI. Three hundred and twenty three patients (5.7%) were false positives (PHT and spoke patients) and 223 patients (3.9%) were walk-ins at the PCI centre. From the remaining 5128 patients who actually underwent pPCI, 2288 patients (45%) were referred via a spoke centre and 2840 patients (55%) via PHT.

Patients from the spoke group were younger, more often smoked, more often had hypercholesterolemia, more often had a previous myocardial infarction (MI), more often presented in Killip class >1 and less often had previous coronary artery bypass grafting (CABG) (Table 1). The median distance from patient's residence to the nearest PCI centre was 38 km (25-49), 28 km (16-41) for the PHT group and 43 km (37-60) for the spoke group ($p<0.001$). The different time intervals for the two groups are presented in Figure 1.

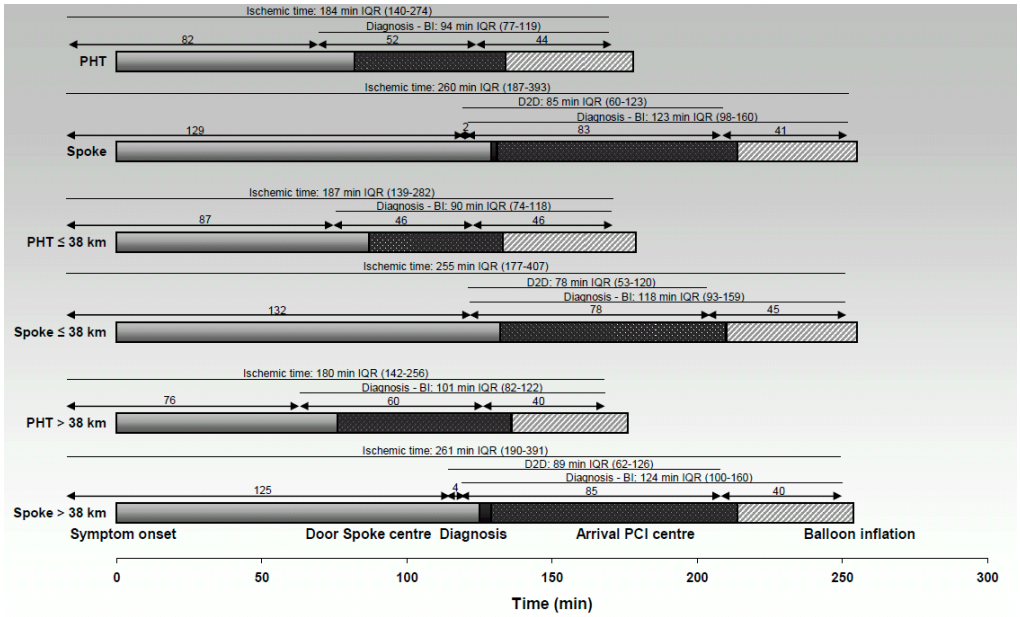

Figure 1. The different time intervals are shown for the total group, for patients living ≤38 km from a PCI centre and for patients living >38 km from a PCI centre. These groups were subdivided for PHT and spoke patients.

Table 1. Baseline characteristics

Characteristic	Total (N=5128)	PHT (N=2840)	Spoke (N=2288)	P
Age years ± SD	62.17±12.14	62.80±12.12	61.40±12.12	<0.001
Male gender	3800/5125 (74.1%)	2110/2838 (74.3 %)	1690/2287 (73.9%)	0.713
Risk factors				
Hypertension	1668/5063 (32.9%)	926/2811 (32.9%)	742/2252 (32.9%)	0.996
Diabetes Mellitus	557/5108 (10.9%)	296/2833 (10.4%)	261/2275 (11.5%)	0.243
Smoking	2433/5015 (48.5%)	1310/2785 (47.0%)	1123/2230 (50.4%)	0.019
Hypercholesterolemia	1085/4852 (22.4%)	563/2682 (21.0%)	522/2170 (24.1%)	0.011
Family history	2058/4928 (41.8%)	1151/2731 (42.1%)	907/2197 (41.3%)	0.542
Killip class >1	346/5098 (6.8%)	171/2831 (6.0%)	175/2267 (7.7%)	0.018
Previous MI	499/5109 (9.8%)	232/2830 (8.2%)	267/2279 (11.7%)	<0.001
Previous PCI	364/5074 (7.2%)	214/2821 (7.6%)	150/2253 (6.7%)	0.203
Previous CABG	132/5119 (2.6%)	84/2837 (3.0%)	48/2282 (2.1%)	0.054
Previous CVA	146/5114 (2.9%)	78/2834 (2.8%)	68/2280 (3.0%)	0.623
TIMI risk score	2.16±1.82 2 (1-3)	2.17±1.84 2 (1-3)	2.15±1.80 2 (1-3)	0.948

PHT:pre-hospital triage group, Spoke:spoke group, SD:standard deviation, MI:myocardial infarction, PCI:percutaneous coronary intervention, CABG:coronary artery bypass graft, CVA:cerebro vascular accident, TIMI:thrombolysis in myocardial infarction.

Table 2. Distance, total ischemic time, indication pPCI and distance of patients home to PCI centre

	PHT	Spoke	P
Total			
Distance (km)*	28.1 (15.9-14.8)	42.6 (37.3-59.9)	<0.001
Ischemic Time (median, IQR, N=2728)	184 (140-274)	260 (187-393)	<0.001
Ischemic Time <3 hrs (%, N=5028)	1285/2784 (46.2%)	601/2244 (26.8%)	<0.001
SO - Diagnosis (median, IQR, N=2531)	82 (47-150)	129 (68-252)	<0.001
Diagnosis - Door PCI (median, IQR, N=1982)	52 (37-68)	83 (59-116)	<0.001
Diagnosis - BI (median, IQR, N=2625)	94 (77-119)	123 (98-160)	<0.001
D2D (median, IQR, N=984)		85 (60-123)	
D2B (median, IQR, N=2664)	44 (30-69)	132 (101-189)	<0.001
Indication pPCI AHA/ACC (%, N=2625)	719/1637 (43.9%)	173/988 (17.5%)	<0.001
Indication pPCI ESC (%, N=2625)	1230/1637 (75.1%)	466/988 (47.2%)	<0.001
Distance home-PCI centre ≤38 km			
Distance (km)*	19.0 (13.1-29.0)	32.6 (26.8-36.0)	<0.001
Ischemic Time (median, IQR, N=1308)	187 (139-282)	255 (177-407)	<0.001
Ischemic Time <3 hrs (N=2522)	850/1908 (44.5%)	171/614 (27.9%)	<0.001
SO - Diagnosis (median, IQR, N=1206)	87 (49-158)	132 (69-259)	<0.001
Diagnosis - Door PCI (median, IQR, N=974)	46 (33-61)	78 (54-114)	<0.001
Diagnosis - BI (median, IQR, N=1240)	90 (74-118)	118 (93-159)	<0.001
D2D (median, IQR, N=285)		78 (53-120)	
D2B (median, IQR, N=1266)	46 (31-74)	127 (98-198)	<0.001
Indication pPCI AHA/ACC (%, N=1245)	484/962 (49.7%)	56/283 (20.1%)	<0.001
Indication pPCI ESC (%, N=1245)	731/962 (76.0%)	149/283 (52.7%)	<0.001
Distance home-PCI centre >38 km			
Distance (km)*	45.9 (41.0-63.0)	49.6 (41.6-66.7)	<0.001
Ischemic Time (median, IQR, N=1420)	180 (142-256)	261 (190-391)	<0.001
Ischemic Time <3 hrs (%, N=2506)	435/876 (49.7%)	430/1630 (26.4%)	<0.001
SO - Diagnosis (median, IQR, N=1325)	76 (45-136)	125 (66-251)	<0.001
Diagnosis - Door PCI (median, IQR, N=1326)	60 (45-79)	85 (61-117)	<0.001
Diagnosis - BI (median, IQR, N=1358)	101 (82-122)	124 (100-160)	<0.001
D2D (median, IQR, N=699)		89 (62-126)	
D2B (median, IQR, N=1398)	40 (27-61)	133 (103-188)	<0.001
Indication pPCI AHA/ACC (%, N=1385)	241/675 (35.7%)	117/710 (16.5%)	<0.001
Indication pPCI ESC (%, N=1385)	488/675 (73.9%)	322/710 (45.4%)	<0.001

*Data expressed as median and IQR.

AHA/ACC:American Heart Association/American College of Cardiology, ESC:European Society of Cardiology, pPCI:primary percutaneous coronary intervention, PHT:pre-hospital triage group, Spoke:spoke group, IQR:interquartile range, SO:symptom onset, PCI:percutaneous coronary intervention, BI:balloon inflation, D2D:door-to-door time, D2B:door-to-balloon time.

Table 3. Angiographic and clinical outcome

	PHT (N=2840)	Spoke (N=2288)	P
Total			
TIMI 3 flow pre-PCI	570/2826 (20.2%)	423/2286 (18.5%)	0.134
TIMI 3 flow post-PCI	2625/2822 (93.0%)	2042/2276 (89.7%)	<0.001
Infarct size ± SD *(IU/l, N=4986)	2188±2187	2575±2259	<0.001
30-day mortality	86/2798 (3.1%)	90/2249 (4.0%)	0.074
One-year mortality	134/2729 (4.9%)	151/2164 (7.0%)	0.002
Distance residence-PCI centre ≤38 km			
TIMI 3 flow pre-PCI	359/1935 (18.6%)	125/626 (20.0%)	0.432
TIMI 3 flow post-PCI	1792/1932 (92.8%)	561/623 (90.0%)	0.030
Infarct size ± SD *(IU/l, N=2482)	2154±2161	2359±2146	0.054
30-day mortality	60/1913 (3.1%)	28/615 (4.6%)	0.096
One-year mortality	98/1878 (5.2%)	41/581 (7.1%)	0.094
Distance residence-PCI centre >38 km			
TIMI 3 flow pre-PCI	211/891 (23.7%)	298/1660 (18.0%)	<0.001
TIMI 3 flow post-PCI	833/890 (93.6%)	1481/1653 (89.6%)	<0.001
Infarct size ± SD *(IU/l, N=2504)	2261±2241	2656±2295	<0.001
30-day mortality	26/885 (2.9%)	62/1634 (3.8%)	0.264
One-year mortality	36/851 (4.2%)	110/1583 (6.9%)	0.007

*peak CK

PHT:pre-hospital triage group, Spoke:spoke group, TIMI:thrombolysis in myocardial infarction, PCI:percutaneous coronary intervention, CK:Creatin Kinase.

Total median ischemic time was 209 min, 184 min for the PHT group and 260 min for the spoke group ($p<0.001$). The percentage of patients treated within three hours of SO was 46.2% in the PHT group compared to 26.8% in the spoke group ($p<0.001$) (Table 2). The time from SO-Diagnosis was shorter for the PHT group as compared to the spoke group (82 vs. 129 min $p<0.001$). The median D2D for the spoke group was 85 min. The D2B was longer for the spoke group as compared to the PHT group (132 vs. 44 min, $p<0.001$).

Significantly more patients of the PHT group were treated according to the most recent guidelines of the AHA/ACC and the ESC as compared to the spoke group (AHA/ACC:PHT 43.9% vs. spoke 17.5%, ESC:PHT 75.1% vs. spoke 47.2%, $p<0.001$ for both comparisons) (Table 2) [8-9].

PHT patients had also better angiographic and clinical outcome. They more often had post procedural TIMI 3 flow (93.0% vs. 89.7%, $p<0.001$), had a smaller infarct size (peak CK: 2188 ± 2187 vs. 2575 ± 2259 IU/l, $p<0.001$) and a lower one-year mortality (4.9% vs. 7.0%, $p=0.002$) (Table 3).

After correction for differences in baseline characteristics, including the difference in distance, PHT was independently associated with an ischemic time of less than three hours (OR: 2.45, 95% CI 2.13 to 2.83), infarct size of less than the median value (OR: 1.19, 95% CI 1.04 to 1.36) and a lower one-year mortality (OR: 0.67, 95% CI 0.50 to 0.91) (Table 4).

Distance to PCI centre

Figure 1 illustrates the time intervals in association with the distance from the patient's residence to the PCI centre. PHT patients had a shorter time from SO-Diagnosis irrespective of distance to the PCI centre. Surprisingly, total ischemic time was even somewhat shorter in the PHT patients living at a distance >38 km as compared to ≤38 km. For both groups however, the time from Diagnosis-Door PCI was longer for patients living at a greater distance from the PCI centre (PHT from 44 min to 55 min, spoke from 78 min to 89 min, $p<0.001$ for both comparisons).

A longer distance led to a decrease in the percentage of patients treated according to the guidelines of the AHA/ACC (≤38 km: 540/1245 (43.4%) vs. >38 km: 358/1385 (25.6%), $p<0.001$) and the ESC (≤38 km: 880/1245 (70.7%) vs. >38 km: 810/1385 (58.5%), $p<0.001$) (Table 2) [8-9].

In patients living ≤38 km from the PCI centre, apart from a higher post procedural TIMI 3 flow in the PHT group, no significant differences in angiographic parameters, infarct size or clinical outcome were found. However, in patients living >38 km away from the PCI centre, PHT patients more often had a higher initial and post procedural TIMI 3 flow, had a smaller infarct size and had a lower one-year mortality compared to the spoke group (Table 3).

DISCUSSION

So far, this is the largest study showing that PHT in the ambulance with immediate transportation to the nearest PCI centre results in a shorter time to treatment, a reduction in infarct size and a better angiographic and clinical outcome as compared to referral via a spoke centre. This was most evident for patients living at greater distance from the PCI centre. In addition, PHT significantly increased the number of patients treated according to the AHA/ACC and the ESC guidelines [8-9]. These results suggest that living at a longer distance from a PCI centre may not negatively influence angiographic and clinical outcomes when PHT is available. Our study showed that 43.9% and 75.1% of the patients fulfil the AHA/ACC respectively the ESC criteria for pPCI when PHT is available. When diagnosis and triage was performed at a spoke centre, only 17.5% (AHA/ACC) and 47.2% (ESC) of the patients were treated according to the guidelines. Figure 1 shows that the largest difference between the groups is seen in the time from SO-Diagnosis. Due to the fact that the ambulance which brought the patient initially to a spoke center was not able to make the infarct diagnosis (no trained personnel, no ECG equipment), diagnosis was only made after arrival of the patient in the spoke centre at a median of 125 min after SO, whereas after PHT, diagnosis was made 49 min (39%) earlier. This earlier diagnosis, together with the early initiation of potent anti-platelet and anti-thrombotic agents in the ambulance (unfractionated heparin, aspirin and clopidogrel), may have led to the higher initial patency and better angiographic outcome in PHT patients [20]. Despite the fact that all efforts were taken to arrange further or a new transport to the PCI centre as soon as possible, the Diagnosis-Door PCI time was considerably longer in the spoke group as compared to the Diagnosis-Door PCI time in the PHT group (83 vs. 52 min,

$p<0.001$) (Figure 1). As a consequence, the D2B time was significantly longer for the spoke group as compared to the PHT group (132 min vs. 44 min, $p<0.001$). These findings correspond with the results of Le May et al. [21].

Table 4. Output multivariate analyses

Treatment within three hours		Infarct size < median		One-year mortality	
Variables	OR (95% CI)	Variables	OR (95% CI)	Variables	OR (95% CI)
Type triage	2.45 (2.13-2.83)	Type triage	1.19 (1.04-1.36)	Type triage	0.67 (0.50-0.91)
Gender	1.21 (1.04-1.41)	Gender	0.67 (0.58-0.78)	Gender	0.90 (0.66-1.21)
Hypertension	1.20 (1.04-1.41)	Hypertension	0.96 (0.84-1.10)	Hypertension	1.42 (1.06-1.92)
Family history	1.04 (0.91-1.18)	Hyperchol	0.99 (0.85-1.16)	Hyperchol	0.63 (0.43-0.93)
DMII	1.01 (0.81-1.26)	Smoking	0.86 (0.75-0.98)	DMII	1.06 (0.72-1.57)
Age	1.03 (1.02-1.04)	Age	1.01 (1.00-1.01)	Age	1.04 (1.02-1.05)
TIMI risk score	0.61 (0.57-0.65)	Previous MI	1.29 (1.01-1.65)	TIMI risk score	1.21 (1.09-1.35)
Previous CABG	0.70 (0.46-1.08)	Previous CABG	1.03 (0.58-1.83)	Family history	0.70 (0.51-0.96)
Previous PCI	1.55 (1.21-1.99)	Previous PCI	1.47 (1.12-1.93)	Previous MI	1.23 (0.90-1.67)
IRV:LAD	1.27 (1.13-1.47)	Killip class >1	0.61 (0.47-0.78)	Pervious CVA	2.29 (1.28-4.10)
Distance	1.00 (1.00-1.00)	IRV:CX	2.10 (0.67-6.64)	Killip class >1	3.07 (1.99-4.72)
		IRV:graft	3.98 (1.02-15.6)	Distance	1.00 (0.99-1.01)
		IRV:LAD	1.85 (0.59-5.81)	IRV:LAD	1.05 (0.80-1.39)
		IRV:RCA	4.05 (1.29-12.7)		
		Distance	0.99 (0.99-1.00)		

CABG, Coronary artery bypass grafting; CX, circumflex; DMII, diabetes mellitus type II; IRV, infarct related vessel; LAD, left anterior descendents; MI, myocardial infarction; RCA, right coronary artery.

Effect of Distance

Our study shows that time to treatment is substantially reduced by pre-hospital triage in the ambulance and shows that incorporating this triage significantly increases the number of patients who are candidates for primary angioplasty instead of thrombolysis according to the guidelines, especially for patients who live further than 38 km away from a PCI centre. These findings suggest that the logistics of arranging diagnosis and immediate transportation is more important than the distance of the patient's residence from a PCI centre: for PHT patients, total ischemic times remained very short despite a longer distance from the PCI centre. A longer distance from the patients' residence to the PCI centre had very limited effect on total ischemic time despite a significantly increased Diagnosis-Door PCI time. This was due to a shorter SO-Diagnosis time.

Other investigators have also studied the effect of distance on clinical outcome in STEMI patients. In a cohort study, Wei et al. demonstrated that patients with a first myocardial infarction who were living at more than nine miles (14.5 km) from the PCI centre had a higher mortality compared to patients who lived closer to the PCI centre [22]. Nevertheless, in our study the effect of distance on outcome was related to the type of patient triage, which was not reported in the study from Wei et al.

According to a recent study, D2B may also be reduced by performing pPCI at a PCI centre without on-site cardiac surgery [23]. However, this study was stopped prematurely and a third arm with routine ambulance triage was lacking [24]. It might therefore be true that the opening of extra PCI centres is not necessary when routine ambulance triage systems are being developed.

Since PHT patients have better outcomes compared to spoke patients more centres should implement the pre-hospital triage for STEMI patients and use ECG equipment with a computerized electrographic algorithm or with telemedicine. It is also important to make patients and general practitioners aware of the fact that PHT with ambulance transport has better outcomes for STEMI patients instead of self-referring, referring via general practitioners or referring via a spoke centre.

Limitations

Several limitations of this study need to be acknowledged. First, since the project was not randomized and dispersed over more than ten years (the percentage of PHT patients increased from 6.0% in 1998, 51.6% in 2004 to 68.7% in 2008), consequently the risk of unknown confounders exists. Some selection of patients has occurred. PHT patients were older and more often lived closer to the PCI centre. During the PHT project, more remote ambulance services started participating, while at the beginning these patients all were transported via a spoke centre.

Second, we did not investigate the effect of fibrinolytics for patients living at great distance. Therefore, we can not state that pre-hospital diagnosis is the best way to treat all STEMI patients living at a great distance, however in our population PHT patients have better outcomes when living at >38 km from a PCI centre compared to patients referred via a spoke centre.

Third, we have no exact numbers of patients who were self-referred or came in by ambulance at the spoke centre. Most patients came in by ambulance at the spoke centre, however these ambulances were not operational with ECG equipment and the EMS personnel was not trained to make STEMI diagnosis. Subsequently, diagnosis was made in the spoke hospital, however first medical contact took place in the ambulance.

Fourth, information of the time of first medical contact is lacking. We expect these times to be the same in both groups, however we do not have solid evidence.

Fifth, although peak CK has been shown to be a reliable parameter for the estimation of infarct size, data on the area under the CK release curve are lacking.

Sixth, we have used the postal codes of patient's residence to calculate the distance to the PCI centre, since the exact location of the place where the patient was picked up by an ambulance was not available.

Finally, more research has to be performed to the favour of PHT for patients living at a long distance from the PCI centre, so more understanding and verification of this improvement can be achieved.

Conclusion

In conclusion, PHT in the ambulance with immediate transportation to the nearest PCI centre is associated with a significantly shorter time to treatment, reduced infarct size and better angiographic and clinical outcome when compared to referral via a nearby spoke centre. This beneficial effect is more apparent with longer distance from the patient's residence to the PCI centre. PHT also significantly increased the percentage of patients that fall within the time window in which pPCI is the preferred treatment according to the AHA/ACC and ESC guidelines. Therefore, PHT may reduce transportation delays in patients who live at a greater distance from the PCI centre.

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CHAPTER 3

FIELD TRIAGE IN THE AMBULANCE VERSUS REFERRAL VIA NON-PERCUTANEOUS CORONARY INTERVENTION CENTRE IN ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION: A SYSTEMATIC REVIEW

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Submitted

ABSTRACT

AIMS

To determine whether direct ambulance transport of ST-elevation myocardial infarction (STEMI) patients to a percutaneous coronary intervention (PCI) hospital (field triage) leads to a lower 30-day mortality compared to transport via a referral non-PCI hospital (referral via a spoke center) in STEMI patients.

METHODS AND RESULTS

We performed a systematic review of interventions. An experienced librarian searched in PubMed, EMBASE.com and The Cochrane Library (via Wiley) from January 1980 to February 2013. Studies that examined field triage and/or referral via a spoke center in STEMI patients treated with primary or facilitated PCI were included. Two authors independently conducted the study selection and data extraction. Multivariable frequency weighted logistic regression analysis was performed to assess the effect of the type of transfer on the outcome measures. We identified 14 RCTs, including 20 transfer groups and 4474 participants. Thirty-day mortality was lower in patients who underwent field triage (3.0%; 95% CI 2.2-4.2) compared to patients who were referred via a spoke center (4.7%; 95% CI 4.0-5.5). In multivariable frequency weighted logistic regression analysis, field triage was independently associated with a lower incidence of 30-day mortality (OR, 0.58; 95% CI 0.37-0.89).

CONLUSION

Field triage compared to referral via a spoke center leads to a lower 30-day mortality in STEMI patients. Therefore, direct ambulance transport to a PCI hospital should become the transfer type for STEMI patients.

INTRODUCTION

It is well known that rapid restoration of coronary blood flow in patients with ST-elevation myocardial infarction (STEMI) is crucial [1] to limit myocardial damage [2-3]. There are two established therapeutic strategies to achieve this: fibrinolytic therapy and primary percutaneous coronary intervention (PCI). The latter is considered more effective [2, 4-7]. However, there is still debate about the time interval during which primary PCI can be recommended. One of the possibilities to shorten delays and maximise the number of patients eligible for primary PCI, is to transport STEMI patients directly to a PCI hospital after pre-hospital triage and diagnosis in which case treatment is started immediately in the ambulance (field triage). However, it is controversial whether such a strategy, when routinely applied, translates in better clinical outcomes. Several observational cohort studies have shown that this strategy can significantly reduce ischemic times and some demonstrated that it leads to improved outcome compared to patients being referred to a referral non-PCI hospital first and later to a PCI hospital (referral via a spoke center) [8-14]. At present, no randomized clinical trials (RCT) have been performed, in which patients were randomized to field triage versus referral via a spoke center. Therefore, in our study a comparison has been made between transfer groups (field triage versus referral via a spoke center) of RCTs in which 30-day mortality was assessed.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs, pseudo RCTs (RCTs with alternate method of allocation) and controlled clinical trials were included.

Types of participants

Studies that examined the following population were included: >18 years, chest pain in the last 24 hours, ECG changes (ST-segment depression and/or ST-segment elevation) and underwent primary PCI or facilitated PCI (early pharmacologic reperfusion therapy followed by PCI). Furthermore, the type of transfer to the PCI hospital (field triage and/or referral via a spoke center) needed to be elucidated and 30-day mortality needed to be one of the outcome measures.

The exclusion criteria were: self-referring patients admitted to the PCI-hospital, in case reperfusion therapy (primary PCI/facilitated PCI and/or fibrinolytic therapy) was presented as combined data and the effect of the different therapies could not be discerned. Self-referring patients were excluded because these patients did not receive pre-hospital triage, diagnosis and treatment, and were not transferred with an ambulance to a PCI center.

Types of interventions

The interventions who were examined in this review included field triage versus referral via a spoke center.

Type of outcome measure

The primary endpoint of this study was all-cause mortality at 30 days.

Search methods for identification of studies

Electronic searches

To identify all relevant publications an experienced librarian (EPJ) performed systematic searches (search date: February 2, 2013) in the bibliographic databases PubMed, EMBASE.com and The Cochrane Library (via Wiley) from January 1980-February 2013. Search terms included controlled terms from MeSH in PubMed, EMtree in EMBASE.com as well as free text terms. Free text terms were only used in The Cochrane library. Search terms expressing 'ST-elevation myocardial infarction patients' were used in combination with search terms comprising 'primary percutaneous coronary intervention' and terms for 'field triage or referral via a spoke center'. The search strategy is available upon request from the primary author.

Searching other resources

Proceedings from the ESC (www.escardio.org), the ACC (www.acc.org), the AHA (www.aha.org), the EUROPCR (www.europcr.com) and the TCT (www.TCTconference.com) were examined over the last five years. Also other systematic reviews with similarly research questions were checked. The references of relevant articles were checked manually. Furthermore, experts in the field were contacted (HS, AWJvtH).

Data collection and analysis

All steps of the data collection and data analysis were conducted by two reviewers independent of one another (SP and EK). This included the identification of studies and data extraction. All disagreements were resolved through consensus.

Selection of studies

Titles and abstracts from the search results were screened and full texts of potentially relevant studies were read and independently assessed for inclusion. Only full text articles were included and the studies needed to be published in Dutch, English or German.

Studies were selected if they met the aforementioned in- and exclusion criteria. In case not all transfer groups of the selected study met the criteria of our study, only the transfer group(s) was/were included which met all criteria. Consequently, only of these transfer groups data was extracted. The most common reason for exclusion of a transfer group was treatment with fibrinolytic therapy.

Data extraction and management

A standardized form was used to extract the qualitative data. The following data were extracted: source, eligibility, methods, participants, outcomes, results, interventions and miscellaneous. The methods included the assessed intervention of the selected study.

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) when considered skewed. Dichotomous data were presented as percentage.

The proportions, percentages and absolute numbers of the primary endpoint were calculated for each transfer group (field triage and referral via a spoke center) separately and all groups combined. The summary effect was calculated by the addition of the absolute numbers of patients that experienced the outcome divided by the total number of patients within the transfer group. Corresponding 95% confidence intervals (CIs) for single proportions were determined according to the Wilson method, which uses asymptotic variance and no continuity correction [15]. The number needed to treat (NNT) was calculated for the outcome measure 30-day mortality.

Modelling. In the univariable analysis, the transfer effect of field triage compared to referral via a spoke center was calculated using a frequency weighted logistic regression analysis. This analysis has the opportunity to give more weight to studies with a high inclusion number and less weight to studies with a low inclusion number. To perform this analysis, the two transfer groups (field triage and referral via a spoke center) were both split into two separate groups. The first group consisted of the patients that did experienced the outcome, as defined by the number of patients presented in the individual studies. The second group consisted of the patients that did not experienced the outcome. Subsequently a logistic regression analysis was performed in which the outcome variable was weighted for the numbers of patients in the transfer groups, since the number of patients differed between the transfer groups.

To correct for differences in baseline characteristics between the two transfer groups a multivariable frequency weighted logistic regression analysis was performed. The variables diabetes mellitus and year of publication were included.

All probability values were 2 tailed, with statistical significance set at 0.05. Analyses were performed with SPSS version 20.0 (SPSS Inc, Chicago, Ill) and STATA version 12.0 (STATA Corp, College Station, Tex). Figures were constructed with GraphPad Prism 5 and Review Manager 5.

Dealing with missing data

It was expected that the amount of missing data was low, since all included studies were performed in the last two decennia. In case of missing data we have contacted the authors of the primary studies. No data were imputed, since we had no individual patient data.

It should be noted that after personal contact with the investigators of several trials [16-20], we have received and used several unpublished data concerning baseline characteristics [16-17] and 30 day mortality [16, 18]. The data of the Assent 4-PCI study were not published previously per transfer group and per type of reperfusion therapy (pPCI and facilitated PCI) [16].

The authors are fully responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

Results of the search and included studies

In total, 14 RCTs were selected in the systematic review (Figure 1) [6, 16-28]. Twenty transfer groups comprising 4474 participants were extracted. Study sample sizes ranged from ten to 988 in the studies (median, IQR: 148 (80-492)) and from five to 988 patients in the included transfer groups (median, IQR: 166 (58-293)).

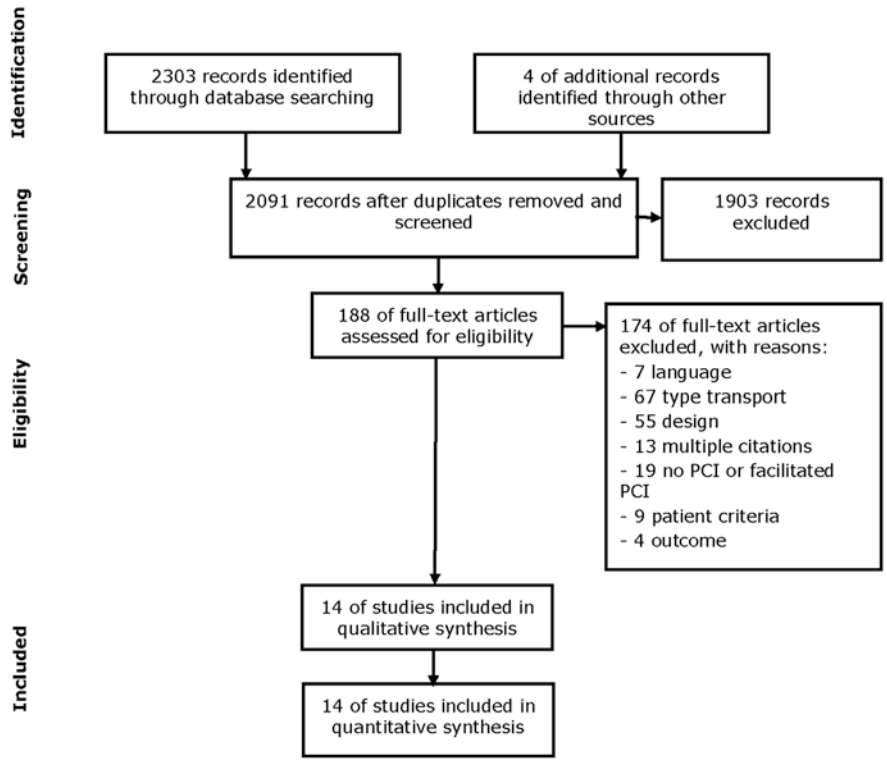

Figure 1. Study flow diagram. Summary of selection process.

Type of transfer and study population

In four studies patients underwent field triage [17-18, 27-28] and in eight studies patients were referred via a spoke center [6, 20-26]. Two studies included both field triage and referral via a spoke center [16, 19]. Nevertheless in these studies patients were not randomized to field triage versus referral via a spoke center, however a post hoc analysis was performed.

Of the 20 transfer groups, in nine transfer groups patients underwent field triage (n=1151) and in 11 transfer groups patients underwent referral via a spoke center (n=3307).

An overview of the baseline characteristics is demonstrated in Table 1 for patients treated with field triage and in Table 2 for patients treated with referral via a spoke center respectively. The type of reperfusion therapy, the prescribed anti-platelet agents as well as time delays are also shown. Time from symptom onset to diagnosis and time from symptom onset to reperfusion therapy were demonstrated as mean ± SD or as median and IQR. Therefore, no overall measurement effect could be examined for the two time intervals.

Effects of interventions

30-day mortality was lower in patients who underwent field triage (3.0%; 95% CI 2.2-4.2) compared to patients who were referred via a spoke center (4.7%; 95% CI 4.0-5.5) (Figure 2A and 2B). Field triage was associated with a reduced risk on 30-day mortality (NNT=59). The unadjusted effect of field triage on 30-day mortality was lower (OR: 0.64, 95% CI 0.44-0.93) compared to referral via a spoke center. In multivariable frequency weighted logistic regression analysis this effect was confirmed (OR: 0.58; 95% CI 0.37-0.89).

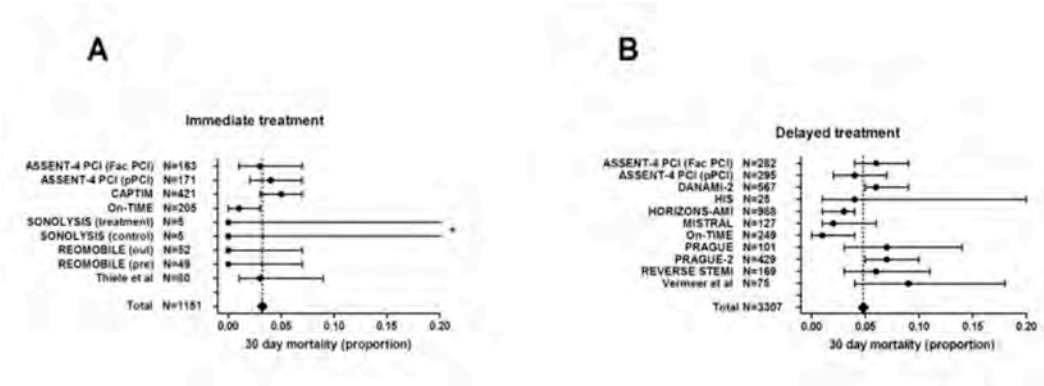

Figure 2. Forrest-tree plot of primary and secondary end point.

Percentages of 30-day mortality with corresponding 95% CIs for single proportions are shown for the field transfer group (A) and for the referral via a spoke center group (B).

CI: confidential interval, Fac: facilitated, pPCI: primary percutaneous coronary intervention, PCI: percutaneous coronary intervention.

* The CI of the SONOLYSIS (treatment) and SONOLYSIS (control) group was both groups 0.00-0.43.

DISCUSSION

Summary of main results

To our knowledge this is the largest performed systematic review which assessed the effect of field triage versus referral via a spoke center on 30-day mortality. The most important finding of our study is that field triage leads to a lower 30-day mortality.

Agreements and disagreements with other studies and reviews

The fact that patients treated with field triage have a lower 30-day mortality is in line with most of the performed studies published so far [8-14]. However, in the post-hoc analysis of the On-TIME study no beneficial effect of field triage compared to referral via a spoke center

Table 1. Baseline characteristics field transfer group

Study name	Primary author and year of publication	Randomization	Included subgroup	N	Medication until procedure	Medication after procedure	Time to diagnosis (min)	Time to reperfusion therapy (min)
ASSENT-4 PCI*	Ross, 2009	Tenecteplase+ heparin+pPCI vs. pPCI	Tenecteplase + heparin+pPCI Enrolment in pre-hospital setting	163	- aspirin - tenecteplase - heparin	clopidogrel	105 (75-172) SO-randomization 107.2±77.8 SO-FMC	223 (180-310) 147.8±80.5 SO-start of treatment
ASSENT-4 PCI*	Ross, 2009	Tenecteplase+ heparin+pPCI vs. pPCI	pPCI Enrolment in pre-hospital setting	171	- aspirin - heparin - GPIIbIIIa inhibitor	clopidogrel	105 (70-160) SO-randomization 99.3±84.0 SO-FMC	203 (154-258) 132.6±90.0 SO-start of treatment
CAPTIM	Bonnefoy, 2002	Alteplase vs. pPCI	pPCI	421	- aspirin - heparin	thienopyridine	108 (76-162) Time to randomization	190 (149-255)
On-TIME*	Van 't Hof, 2006	Early tirofiban+pPCI vs. late tirofiban+pPCI	Early tirofiban+pPCI vs. late tirofiban+PCI Enrolment in ambulance	209	- aspirin - heparin - tirofiban or placebo	- aspirin - clopidogrel - beta blocker - statin - ACE inhibitor	106.3±93.6 75 (47.5-131) (n=205)	211.2±132.2 176.5 (144-237) (n=178)
SONOLYSIS*	Slikkeveer (treatment), 2012	Microbubles with 3-D guided high mechenical index pulses+pPCI vs. placebo with ultrasound+pPCI	Microbubles with 3-D guided high mechenical index pulses+pPCI	5	- aspirin - heparin - alteplase - micro bubble Luminity + 0.9% saline - heparin	Unknown, no standard therapy	85±55 (mean±SD)	178±57 (mean±SD)

					- GP IIbIIIa inhibitor			
SONOLYSIS*	Slikkeveer (control), 2012	Microbubles with 3-D guided high mechenical index pulses+pPCI vs. placebo with ultrasound+pPCI	Placebo with ultrasound+ pPCI	5	- aspirin - heparin - alteplase - 0.9%saline - heparin - GPIIbIIIa inhibitor	Unknown, no standard therapy	118±78 (mean±SD)	226±87 (mean±SD)
REOMOBILE*	Pels (out-of-hospital abciximab), 2008	Out-of-hospital abiciximab+PCI vs. periprocedural abciximab+PCI	Out-of-hospital abiciximab+PCI	52	-aspirin - heparin - clopidogrel - abciximab	- aspirin - heparin	-	-
REOMOBILE*	Pels (preprocedural abciximab), 2008	Out-of-hospital abiciximab vs. periprocedural abciximab	Periprocedural abiciximab+PCI	49	- aspirin - heparin - clopidogrel - abciximab	- aspirin - heparin	-	-
-	Thiele, 2005	Reteplase vs. reteplase+pPCI	Reteplase+pPCI	82	- aspirin - heparin - abciximab - reteplase	- aspirin - clopidogrel - beta-blockers - ACE inhibitors - statins - abciximab infusion	30 (21-38) SO-call mobile care unit 50 (21-103) Call mobile care unit-arrival at scene 9 (7-12) Arrival at scene-first reteplase bolus	50 +9+30+90+42+12+63 (all medians)

*After contact with the corresponding author unpublished data has been received and used.

ACE: angiotensin-converting-enzyme, FMC: first medical contact, GPPIIbIIIa inh: glycoprotein IIbIIIa inhibitor, min: minutes, PCI: percutaneous coronary intervention, pPCI: primary percutaneous coronary intervention, SD: standard deviation, SO: symptom onset.

Table 2. Baseline characteristics referral via a spoke center group

Study name	Primary author and year of publication	Randomization	Included subgroup	N	Medication until procedure	Medication after procedure	Time to diagnosis (min)	Time to reperfusion therapy (min)
ASSENT-4 PCI*	Ross, 2009	Tenecteplase+ heparin+pPCI vs. pPCI	Tenecteplase+ heparin+pPCI Enrolment in non-PCI hospital	282	- aspirin - tenecteplase - heparin	clopidogrel	130 (86-190) SO-randomization 107.9±74.7 SO-FMC	272 (229-350) 162.1±81.4 SO-start of treatment
ASSENT-4 PCI*	Ross, 2009	Tenecteplase+ heparin+pPCI vs. pPCI	pPCI Enrolment in non-PCI hospital	296	- aspirin - heparin - GPIIbIIIa inhibitor	clopidogrel	135 (90-185) SO-randomization 120.8±158.2 SO-FMC	273 (227-345) 162.7±98.8 SO-start of treatment
DANAMI-2	Andersen, 2003	Alteplase vs. pPCI	pPCI Enrolment in non-PCI hospital	567	- aspirin - beta-blocker - heparin - GPIIbIIIa inhibitor	- ticopidine or clopidogrel	107 (60-205)+22 (15-35) SO-admission+ admission-randomization	224 (171-317)
HIS	Dieker, 2006	Abciximab+pPCI vs. on-site fibrin-specific thrombolytic therapy	Abciximab facilitated primary angioplasty	25	- aspirin - enoxaparin - abciximab - heparin	- aspirin - enoxaparin	130 (81-146)	230 (195-250) Pain-angioplasty
HORIZONS-AMI	Wöhrle, 2010	Bivalirudin+pPCI vs. Unfractioned heparin+GPIIbIIIa receptor inhibitor +pPCI	Bivalirudin+pPCI vs. Unfractioned heparin+GPIIbIIIa receptor inhibitor+pPCI Enrolment with transfer	988	- aspirin - clopidogrel or ticlopidine - bivalirudin or heparin - abciximab or eptifibatide	- aspirin - clopidogrel or ticlopidine	-	272 (IQR -)

MISTRAL	Ohlmann, 2012	Abciximab in ambulance+pPCI vs. abciximab in-hospital+pPCI	Abciximab in ambulance+ pPCI	127	- aspirin - heparin - abciximab	- abciximab - clopidogrel	79 (47-137)	190 (142-239)
On-TIME*	Van 't Hof, 2006	Early tirofiban+pPCI vs. late tirofiban+pPCI	Early tirofiban+pPCI and late tirofiban+pPCI Enrolment in non-PCI hospital	258	- aspirin - heparin - tirofiban or placebo	- aspirin - clopidogrel - beta blocker - statin - ACE inhibitor	118.3±83.5 106 (62-149) (n=249)	226.8±81.6 208 (175-264) (n=223)
PRAGUE	Widimsky, 2000	Streptokinase vs. streptokinase+pPCI vs. pPCI	pPCI	101	- lysin salicylate - heparin	- ticlopidine - fraxiparin	120+15	215
PRAGUE-2	Widimsky, 2003	Streptokinase vs. pPCI	pPCI	429	- aspirin - heparin	- clopidogrel - fraxiparin - GPIIbIIIa inhibitor	183±162 (mean±SD) SO-randomization	277 (SD -)
REVERSE STEMI	Zhang, 2011	pPCI with interventionalist vs. pPCI with patient-transfer	pPCI with patient-transfer	169	- aspirin - clopidogrel - GPIIbIIa inhibitor	- aspirin - clopidogrel	-	-
-	Vermeer, 1999	Alteplase vs. alteplase+rescue PCI vs. pPCI	pPCI	75	- acetylsalicylic acid - heparin	- aspirin - heparin - nitrate	130 ± - (mean)	85±25 (mean±SD)

*After contact with the corresponding author unpublished data has been received and used.

ACE: angiotensin-converting-enzyme, FMC: first medical contact, GPPIIbIIIa inh: glycoprotein IIbIIIa inhibitor, min: minutes, PCI: percutaneous coronary intervention, pPCI: primary percutaneous coronary intervention, SD: standard deviation, SO: symptom onset.

was demonstrated [19]. This might be explained by the fact that in this trial the amount of included patients was not sufficient to reach significance. In the post-hoc analysis of the Assent 4-PCI study also no significant difference was found between the two transfer groups, although mortality was assessed at 90 days instead of 30 days [16]. Furthermore, there were some studies who demonstrated no need to transfer patients for pPCI from a non-PCI centre, however in these studies transfer patients were compared to patients already presenting at a tertiary PCI center without the need for transfer [21-22, 29-30].

Our results are in contrast with the publication of Brooks et al., in which the conclusion of the systematic review and meta-analysis was that there is insufficient evidence to support the effectiveness of field triage compared to referral via a spoke center in STEMI patients concerning mortality [31]. However, they applied different criteria for considering studies: besides RCTs they also included prospective observational cohort studies and they did not include studies with one transfer arm of interest. Furthermore, their endpoint was a composite of in-hospital and 30-day mortality. Therefore, only one study was included in both reviews.

Potential biases in the review process

We have not chosen to include prospective observational cohort studies besides RCTs, pseudo RCTs and controlled clinical trials, since these studies are biased in multiple ways. After all in our study only RCTs were included, because no pseudo RCTs and controlled clinical trials were performed.

Limitations

Several limitations of our systematic review should be noted. Firstly, since in this review transfer groups of studies were compared instead of RCTs, no meta-analysis could be performed and the comparison made in our study was non randomized. Considering this result, for the future RCTs are warranted. However it is highly unlikely that new RCTs investigating this topic will be designed and subsequently approved by an ethical committee, because referral via a spoke center is usually coincided with prolonged treatment delays and therefore in conflict with the current ESC and AHA/ACC guidelines [32-33]. Hence, our study design seems to be the best choice to assess the research question of our study. Secondly, only a few variables were included in the weighted multivariable analysis since 20 transfer groups were included. The effect of time from symptom onset to diagnosis/randomization and time from symptom onset to reperfusion could not be included, because the data from the selected studies in this review did not allow for a detailed exploration of the relationship between the relative benefit of the type of transfer and the abovementioned time intervals. Therefore, we are unable to pronounce upon maximum time delays for the types of transfer. Thirdly, because no more than 14 studies were included, sensitivity analyses were not performed.

Conclusion

In conclusion, field triage compared to referral via a spoke center leads to a lower 30-day mortality in STEMI patients. Therefore, direct ambulance transport to a PCI hospital should become the transfer type for STEMI patients. Future studies should determine the optimal timing for field triage versus referral via a spoke center.

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CHAPTER 4

THE INFLUENCE OF RESIDENTIAL DISTANCE ON TIME TO TREATMENT IN ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS

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ABSTRACT

AIMS

To evaluate the relation between residential distance and total ischaemic time in patients with acute ST-elevation myocardial infarction (STEMI).

METHODS

STEMI patients were transported to the Isala Hospital Zwolle with the intention to perform primary percutaneous coronary intervention PCI (pPCI) from 2004 until 2010 (n=4149). Of these, 1424 patients (34 %) were referred via a non-PCI 'spoke' centre ('spoke' patients) and 2725 patients (66 %) were referred via field triage in the ambulance (ambulance patients).

RESULTS

A longer residential distance increased median total ischaemic time in 'spoke' patients (0–30 km: 228 min, >30-60 km: 235 min, >60-90 km: 264 min, p<0.001), however not in ambulance patients (0–30 km: 179 min, >30-60 km:175 min, >60-90 km: 186 min, p=0.225). After multivariable linear regression analysis, in 'spoke' patients residential distance of >30-60 km compared with 0–30 km was not independently associated with ischaemic time; however, a residential distance of >60-90 km (exp (B)=1.11, 95% CI 1.01-1.12) compared with 0–30 km was independently related with ischaemic time. In ambulance patients, residential distance of >30-60 and >60-90 km compared with 0–30 km was not independently associated with ischaemic time.

CONCLUSION

A longer distance from the patient's residence to a PCI centre was associated with a small but significant increase in time to treatment in 'spoke' patients, however not in ambulance patients. Therefore, referral via field triage in the ambulance did not lead to a significant increase in time to treatment, especially at long distances (up to 90 km).

INTRODUCTION

Strategies to reduce time delays in ST-segment elevated myocardial infarction (STEMI) patients are currently of great interest, since shorter time delays improve outcome [1–5]. Transportation delay is a time delay which is mainly dependent on the type of transport, mode of referral, geographical area, weather conditions, traffic and distance. In urban areas, ambulance transport is the transport of choice and in rural areas air transport usually facilitates the transfer of STEMI patients. Previous studies have shown that optimising logistics by field triage in the ambulance can help to reduce time to treatment and improve outcomes compared to referral via a non-percutaneous coronary intervention (PCI) spoke centre (peripheral centre) [5–12]. Only a few published data exist on the effect of geographical area [8, 13–16], weather conditions [16], traffic [16] and distance [5, 16–19] on time to treatment.

In the Netherlands, distance to a PCI centre (hub centre: specialised central interventional centre) was one of the reasons to expand primary PCI to more hospitals, including those without on-site cardiac surgery. It was expected that with more PCI centres transportation delay might decrease and clinical outcomes might improve. However, recently Concannon et al. demonstrated that introducing new PCI centres did not help patients gain access to timely PCI [20]. Therefore, we have investigated the relation between residential distance and total ischaemic time in STEMI patients referred to a large tertiary PCI centre. In addition, the effect of residential distance on total ischaemic time was assessed in patients who were referred via a non-PCI spoke (spoke) centre and in patients referred via field triage in de ambulance.

METHODS

Population

Since the early 1990s, STEMI patients referred to the Isala Hospital Zwolle were treated by primary PCI (pPCI). To improve the logistics of STEMI patients, the field triage project was initiated. This has gradually been implemented in the region, starting in 1998 until all ambulances were part of the field triage project. During the project all consecutive STEMI patients who were transported to the PCI centre with the intention to perform pPCI, from 2004 until 2010, were prospectively registered in a dedicated database. Criteria for the diagnosis of STEMI were: 1) history of cardiac symptoms of at least 30 min in the last 12 h or between 12 and 24 h if they had persistent symptoms with evidence of ongoing ischaemia; 2) elevated levels of creatine kinase (CK) or creatine kinase-MB (CK-MB) and 3) concurrent electrocardiogram (ECG) changes: ST-segment elevation of >0.1 mV in at least two adjacent electrocardiogram leads [21].

The residential distance to the nearest PCI centre via the motorway was computerised using the postal codes of the patient's residence and the PCI centre. Subsequently three groups were formed according to distance: 1) 0–30 km, 2) >30-60 km and 3) >60-90 km. Furthermore, a subdivision by type of triage was performed. Patients were transferred via a

referral spoke centre in the network (spoke group) or via field triage in the ambulance (ambulance group).
Patients were excluded if the distance from the patient's residence to the PCI centre could not be assessed or was >90 km (outer boundary of referring area).

Triage for pPCI

We hypothesised that the effect of distance on outcome might be different for spoke patients versus ambulance patients, as referral logistics are different between the two groups. Spoke patients are transported twice: the first time to bring the patient from their residence to the nearest spoke centre and a second time to bring the patient to the PCI centre after diagnosis of myocardial infarction in the spoke centre. Conversely, ambulance patients are transported only once via the shortest and fastest possible way and immediately after myocardial infarction diagnosis at the patient's residence.
Spoke group: If the ambulance was not equipped with field triage equipment, the ambulance went to the nearest spoke centre where diagnosis and triage was performed. If the ECG performed upon arrival was diagnostic for STEMI, patients were transported to the catheterisation laboratory of the PCI centre as soon as possible, preferably by using the same ambulance.
Ambulance group: The algorithm of field triage has been described previously [17]. In brief, after patients had dialled the emergency number, they were triaged in the ambulance. An ECG was performed by highly trained paramedics followed by interpretation by the computerised algorithm. If a diagnosis of STEMI was made, the ambulance went straight to the catheterisation laboratory of the PCI centre, bypassing the emergency departments of nearby spoke centres.
Walk-ins at the PCI centre were excluded since they did not receive field triage.

pPCI procedure

In both situations, the staff of the catheterisation laboratory of the PCI centre was pre-informed about the estimated time of arrival of the patient and was activated well before the arrival of the patient. If the staff lived more than 30 min away from the PCI centre, they had to stay in the PCI centre when on call. All patients were treated pre-hospital with an intravenous bolus of 5000 IU of unfractionated heparin and 500 mg aspirin intravenously. During the study period the administration of clopidogrel on top of aspirin and heparin as pre-hospital treatment was implemented at 1 July 2006. The administration of GP IIb/IIIa blockers in the pre-hospital phase was left at the discretion of the referring physicians.

Time intervals

Four different time intervals were evaluated: 1) Time from symptom onset to infarct diagnosis (time of diagnostic ECG) either in the ambulance or at a spoke centre (symptom onset to diagnosis); 2) Time from diagnosis till arrival at the PCI centre (diagnosis to door PCI); 3)

Time from arrival at the PCI centre to balloon inflation (door to balloon) and 4) Total ischaemic time defined as the time from symptom onset to balloon inflation.
Patients were excluded if the total ischaemic time could not be assessed.

Statistical analysis

Statistical analysis was performed with SPSS 20.0. Continuous data were expressed as mean ± SD or median and interquartile range. Categorical data were presented as percentages. A Kruskal-Wallis test was used for continuous data, since they were non-Gaussian distributed. A Pearson's Chi-square test was used for categorical data. The relationship between total ischaemic time and residential distance for each patient was assessed using Spearman's correlation. Linear regression analysis was performed to estimate the effect of residential distance on total ischaemic time. To assess whether the mode of referral might interfere with the relationship between residential distance and total ischaemic time, interaction testing was performed. For the regression analysis and the interaction testing total ischaemic time was log transformed, since this time interval was non-Gaussian distributed.
All above-described statistical tests were two-sided. In all statistical analyses p values <0.05 were considered to be statistically significant.
The study was conducted according to the principles of the Declaration of Helsinki and the protocol was approved by the local institutional review board. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

From 2004 until 2010, 5285 patients were referred to our hospital with the intention to perform pPCI. A total of 349 patients (6.6%) were walk-ins at the PCI centre, in 184 patients the residential distance could not be assessed (3.5%) and 603 patients (11.4%) were excluded because the total ischaemic time could not be assessed.
Of the remaining 4149 patients, 1424 patients (34 %) were referred via a spoke centre and 2725 (66%) via field triage in the ambulance. Figure 1a and b illustrate the distance from the patient's residence to the PCI centre for the spoke group and the ambulance group on a map of the Netherlands. Spoke patients mainly lived between 30–90 km away from the PCI centre, while ambulance patients mostly lived within a residential distance of 0–60 km.
There was a significant interaction effect between residential distance and type of triage on total ischaemic time ($p=0.038$). Therefore, the results are presented separately for the two groups.

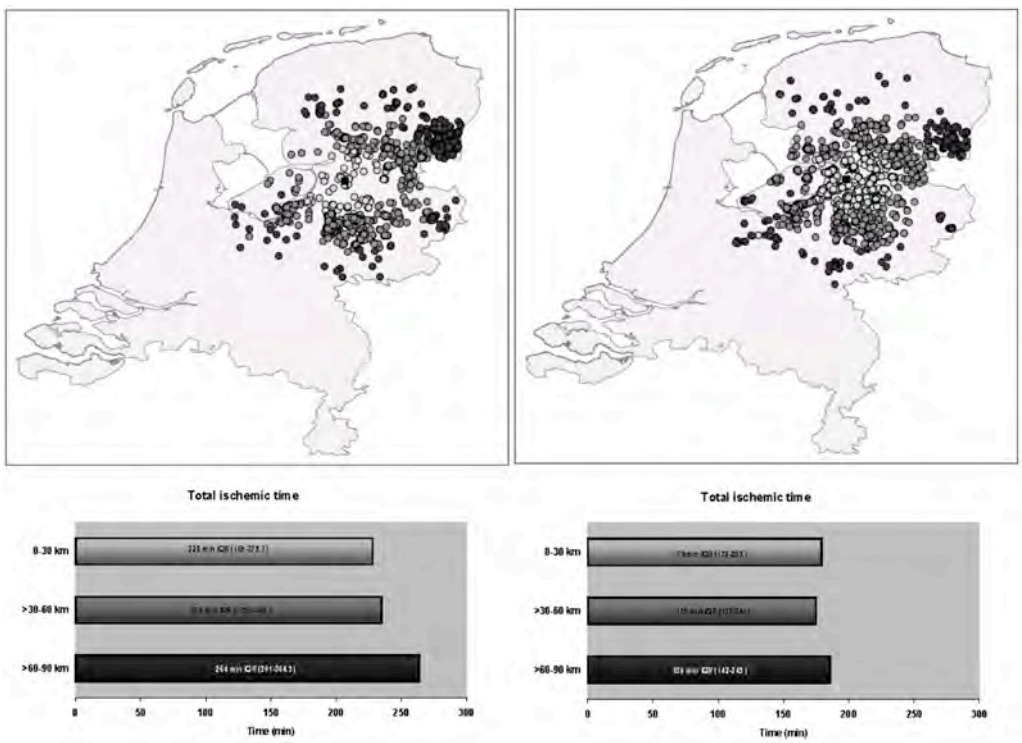
Spoke group

The baseline characteristics of spoke patients are described in Table 1. The presence of Killip class >1 and incidence of previous CABG decreased with distance from patient's residence to the PCI centre. The correlation between residential distance and total ischaemic time was

weak although significant (r=0.078, p=0.003). Furthermore, median total ischaemic time increased with distance as well as the other described time intervals (Table 2 and Figure 1A). After multivariable linear regression analysis residential distance of >30-60 km (exp (B)=0.98, 95% CI 0.90-1.06) compared with 0–30 km was not independently associated with ischaemic time, however a residential distance of >60-90 km (exp (B)=1.11, 95% CI 1.01-1.12) compared with 0–30 km was independently related with ischaemic time.

Ambulance group

The baseline characteristics of ambulance patients are described in Table 1. The correlation between residential distance and total ischaemic time was not significant (r=0.017, p=0.382). The time from diagnosis to door PCI increased (p<0.001) and the door to balloon time decreased (p<0.001) (Table 2 and Figure 1B). After multivariable linear regression analysis a residential distance of >30-60 km (exp (B)=1.00, 95 % CI 0.97-1.04) and of >60-90 km (exp (B)=1.06, 95% CI 0.99-1.13) compared with 0–30 km were not independently related to ischaemic time.



A **B**

Figure. 1 Distribution of residential distance and total ischaemic time.

Above the distance from the patient's residence to the PCI centre is illustrated on a map of the Netherlands for the spoke group (A) and the ambulance group (B). Black dot: Isala Hospital Zwolle, light grey dots: patients living 0–30 km from the PCI centre, grey dots: patients living >30-60 km from the PCI centre, dark grey dots: patients living >60-90 km from the PCI centre. Below the total ischaemic time is shown for the spoke group (A) and the ambulance group (B) for patients living 0–30 km, >30-60 km and >60-90 km from a PCI centre.

Table 1. Baseline characteristics

	Spoke group				Ambu group			
	Distance 0-30 km	Distance >30-60 km	Distance >60-90 km	P-value	Distance 0-30 km	Distance >30-60 km	Distance >60-90 km	P-value
Characteristic	**n=134**	**n=978**	**n=312**		**n=1246**	**n=1263**	**n=216**	
Age years ± SD	64.41 ± 12.94 (n=134)	63.48 ± 12.81 (n=978)	62.59 ± 11.76 (n=312)	0.350	63.52 ± 13.00 (n=1246)	63.40 ± 12.28 (n=1263)	63.02 ± 12.09 (n=216)	0.813
Male gender	98/134 (73.1%)	674/978 (68.9%)	226/312 (72.4%)	0.358	921/1246 (73.9%)	943/1263 (74.7%)	159/216 (73.6%)	0.891
Previous MI	16/131 (12.2%)	111/975 (11.4%)	36/312 (11.5%)	0.961	110/1243 (8.8%)	118/1254 (9.4%)	12/215 (5.6%)	0.189
Previous CABG	7/131 (5.3%)	32/978 (3.3%)	3/312 (1.0%)	0.026	37/1245 (3.0%)	36/1259 (2.9%)	7/215 (3.3%)	0.947
Previous PCI	13/131 (9.9%)	93/976 (9.5%)	33/310 (10.6%)	0.846	125/1245 (10.0%)	97/1256 (7.7%)	15/215 (7.0%)	0.078
Previous CVA	5/131 (3.8%)	29/978 (3.0%)	9/312 (2.9%)	0.855	39/1245 (3.1%)	37/1255 (2.9%)	7/215 (3.3%)	0.950
Hypertension	44/131 (33.6%)	362/974 (37.2%)	111/311 (35.7%)	0.686	437/1241 (35.2%)	420/1251 (33.6%)	63/215 (29.3%)	0.220
Diabetes Mellitus	14/131 (10.7%)	118/975 (12.1%)	42/312 (13.5%)	0.690	131/1245 (10.5%)	128/1258 (10.2%)	18/216 (8.3%)	0.617
Hypercholesteremia	31/129 (24.0%)	209/954 (21.9%)	77/305 (25.2%)	0.455	254/1208 (21.0%)	245/1220 (20.1%)	42/209 (20.1%)	0.837
Smoking	57/130 (43.8%)	381/955 (39.9%)	144/305 (47.2%)	0.070	512/1227 (41.7%)	541/1243 (43.5%)	83/212 (39.2%)	0.410
Anterior MI	56/132 (42.4%)	409/970 (42.2%)	139/307 (45.3%)	0.627	489/1205 (40.6%)	530/1229 (43.1%)	95/212 (44.8%)	0.315
Killip class >1	12/133 (9.0%)	91/973 (9.4%)	11/311 (3.5%)	0.004	96/1243 (7.7%)	83/1260 (6.6%)	15/216 (6.9%)	0.540
TIMI risk score (mean ± SD, median (IQR))	3.09 ± 2.29 3.0 (1.0-5.0) (n=119)	3.16 ± 2.27 3.0 (1.0-5.0) (n=839)	2.95 ± 2.09 3.0 (1.0-4.0) (n=214)	0.592	2.79 ± 2.16 3.0 (1.0-4.0) (n=1108)	2.78 ± 2.09 3.0 (1.0-4.0) (n=1144)	2.81 ± 2.46 2.0 (1.0-4.0) (n=194)	0.806
GPIIBIIIA blocker*	43/134 (32.1%)	278/978 (28.4%)	73/312 (23.4%)	0.109	218/1246 (17.5%)	219/1263 (17.3%)	26/216 (12.0%)	0.129

*administered in the acute phase

CABG: coronary artery bypass graft, CVA: cerebro vascular accident, D2B: door-to balloon, IQR: interquartile range, GPIIBIIIA: Glycoprotein IIBIIIA; MI: myocardial infarction, PCI: percutaneous coronary intervention, SD: standard deviation, SO: symptom onset, TIMI: thrombolysis in myocardial infarction.

Table 2. Time intervals

	Spoke group				Ambu group			
	Distance 0-30 km	Distance >30-60 km	Distance >60-90 km	P-value	Distance 0-30 km	Distance >30-60 km	Distance >60-90 km	P-value
Time intervals	**n=134**	**n=978**	**n=312**		**n=1246**	**n=1263**	**n=216**	
Ischemic time (median, IQR)	228 (169-375.3) (n=134)	235 (175.8-320) (n=978)	264 (201-364.5) (n=312)	<0.001	179 (132-253) (n=1246)	175 (137-244) (n=1263)	186 (142-245) (n=216)	0.225
SO-Diagnosis (median, IQR)	86 (48-217) (n=119)	112 (62-196) (n=859)	137.5 (72.3-223) (n=268)	0.039	77 (44-142) (n=1154)	74.5 (42-133) (n=1186)	71 (39-135) (n=205)	0.211
Diagnosis-Door PCI (median, IQR)	73.5 (523-109.5) (n=120)	74 (56-100) (n=861)	93 (74.5-118) (n=273)	<0.001	41 (30-53) (n=1107)	53 (42-65.5) (n=1169)	66 (50-82.3) (n=205)	<0.001
D2B (median, IQR)	40 (25-69) (n=114)	41 (27-60) (n=844)	35 (25-53) (n=290)	0.034	50 (35-75) (n=1071)	42 (29-60) (n=1125)	40 (29-60.3) (n=190)	<0.001

D2B: door-to balloon, IQR: interquartile range, SO: symptom onset.

DISCUSSION

Our study is the largest of its kind demonstrating that living further away from a PCI centre increases time to treatment in patients referred via a spoke centre, but to a lesser extent in patients who were immediately transported after field triage in the ambulance. Overall the increase in median total ischaemic time with longer residential distance was modest (30–90 km: 36 min (spoke) vs. 7 min (ambulance)). This limited effect of residential distance on total ischaemic time can partly be explained by the reduced door to balloon time with longer residential distance. A longer transportation delay gives the opportunity to prepare the cath-lab for PCI, after a call from the ambulance or spoke centre. These findings imply that a substantial increase in residential distance can be covered with only a modest increase in transportation time and suggests that prolonged transportation distances have a limited effect on outcome, when other components of the total ischaemic time are optimally organised. This was clearly found when patients were diagnosed and immediately transported after prehospital triage in the ambulance: for 30–60 km residential distance from the PCI centre transportation took 74 min (median) for a spoke patient as compared with 53 min (median) for an ambulance patient (Table 2). In this regard it should be emphasised that residential distance as mentioned in the study is calculated as the shortest distance by motorway from the patient's residence to the PCI centre. Ambulance-triaged patients were transported via this shortest distance whereas spoke patients travelled longer distances. Firstly, on the way to the spoke centre and secondly, on the way from the spoke centre to the PCI centre, consequently resulting in a longer time to diagnosis and a long inter-hospital transportation time.

Until now, only few data are available on the relation between residential distance and total ischaemic time. Recently we showed that field triage in the ambulance may reduce the negative effect of living at a longer distance from a PCI centre [5]. Beri et al. have demonstrated that longer distances did not result in any significant transfer delay [22]. However, they did not investigate the effect of short versus long distance, but the effect of pPCI versus fibrinolytic therapy at long distance.

Besides referring patients directly after field triage in the ambulance to a PCI centre, expansion of primary PCIs to more hospitals is also a widely discussed option to improve treatment delay [20, 23].

We believe expansion of PCI centres may play less of a role in the overall improvement of timely treatment of STEMI patients, since our results demonstrate that residential distance is only weakly associated with total ischaemic time if patients are transferred via field triage in the ambulance. Furthermore, the number, availability and expertise of the interventional cardiologists plays also an important role in providing timely access to PCI as well as the expertise of ambulance personnel. In addition, in the future more attention is needed for changes in PCI capacity and the effects of these changes on outcome measures as well as on the selection of high-risk patients for transfer.

Limitations

Firstly, the postal code of the patients' residence was used as a proxy for the place where the ambulance picked up the patient. Information on the exact distance between the patient's residence and the place where the ambulance picked up the patient was not available. However, a random sample of 716 cases revealed that >80 % of the patients were picked up <5 km from their residence. Secondly, since the project was not randomised and was spread over more than 10 years, the risk of unknown confounders exists. Thirdly and perhaps the most important limitation is the fact that our study was performed in a small country with a flat landscape where ambulance triage for STEMI patients is optimised, where distances between the patient's residence and PCI centres are surmountable to treat most patients according to the ACC/AHA and ESC guidelines and where traffic and weather conditions are no major issue. More research is needed to investigate whether comparable results can be achieved in other areas of the world.

Conclusions

A longer distance from the patient's residence to a PCI centre was associated with a small but significant increase in time to treatment in patients referred via a non-PCI spoke centre, although this association was weak. In patients who were referred via field triage in the ambulance there was no significant association between residential distance and time to treatment. Therefore, referral via field triage in the ambulance did not lead to a significant increase in time to treatment, especially at long distances (up to 90 km).

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CHAPTER 5

THE INFLUENCE OF SYSTEM DELAY ON 30-DAY AND LONG TERM MORTALITY IN PATIENTS WITH ANTERIOR VERSUS NON-ANTERIOR ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

AIMS

To evaluate the relation between system delay and 30-day and long term mortality in patients with anterior versus non-anterior ST-elevation myocardial infarction (STEMI).

METHODS

We conducted a prospective observational cohort study. STEMI patients who were transported to the Isala hospital Zwolle and underwent primary percutaneous coronary intervention (pPCI) from 2005 until 2010 were included. These patients were divided in quartiles of system delay (time from first medical contact until reperfusion therapy): Q1-Q4.

RESULTS

In total, 3041 patients were included in our study. Forty one percent (n=1253) of the patients had an anterior myocardial infarction (MI) and 59% percent of the patients (n=1788) had a non-anterior MI. Only in patients with an anterior MI, prolonged system delay was associated with a higher mortality (30-day Q1: 2.6%, Q2: 3.1%, Q3: 6.8%, Q4: 7.4%, p=0.001; long term Q1: 12.8%, Q2: 13.7%, Q3: 24.1%, Q4: 22.6%, p<0.001). After multivariate adjustment prolonged system delay was associated with a higher 30-day and long-term mortality in anterior MI patients (30 day Q2: HR 1.18 95% CI (0.46-3.00), Q3: HR 2.45 95% CI (1.07-5.63), Q4:HR 2.25 95% CI (0.97-5.25)); long term Q2: HR 1.09 95% CI (0.71-1.68), Q3: HR 1.68 95% CI (1.13-2.49), Q4: HR 1.55 95% CI (1.03-2.33)), but not in patients with a non-anterior MI.

CONCLUSIONS

Prolonged system delay significantly increased short as well as long term mortality in patients with an anterior MI. This effect was not demonstrated in patients with a non-anterior MI. Therefore it is of the greatest importance to minimize system delay in patients who present with an anterior MI.

INTRODUCTION

As stated in the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) and of the European Society of Cardiology (ESC) it is crucial to perform rapid reperfusion therapy in patients with ST-segment elevated myocardial infarction (STEMI) [1-2], because every minute of delay in these patients affects mortality [3]. Therefore, currently time delays like system delay, patient delay, transportation delay, door-in-door-out (DIDO) time and door-to-balloon (D2B) time are of great interest in STEMI patients [4-8]. System delay, defined as time from first medical contact (FMC, i.e. EMS call) to reperfusion therapy, is a relatively new time delay which can be optimized by optimizing the system. As demonstrated by Terkelsen et al. system delay was independently associated with mortality [4]. Since we hypothesised that this effect would be the most apparent in high risk patients, we have investigated the effect of system delay on 30-day and long term mortality in patients with an anterior myocardial infarction (MI) versus a non-anterior MI.

METHODS AND ANALYSIS

Population

All consecutive STEMI patients who were transported to our percutaneous coronary intervention (PCI) centre with the intention to perform pPCI from 2005 until 2010, were prospectively registered in a dedicated database. Criteria for the diagnosis of STEMI were: (1) history of cardiac symptoms of at least 30 minutes in the last 12 hours or between 12 and 24 hours if they had persistent symptoms with evidence of ongoing ischemia (2) elevated levels of Creatin Kinase or Creatin Kinase-MB and (3) concurrent electrocardiogram changes: ST-segment elevation of >0.1mV in at least two adjacent electrocardiogram leads [9].

Infarct size was calculated as the peak level of Creatin Kinase (peak CK) within 24 hours after admission [10]. The municipal registration in the Netherlands was consulted for the mortality of all patients in this study.

The included population was divided in four groups according to the quartiles of system delay (Q1, Q2, Q3 and Q4). System delay was defined as the time from FMC, i.e. EMS call to reperfusion therapy. Four other time intervals were also evaluated 1. Symptom onset (SO)-diagnosis: time from SO to indication MI (time diagnostic electrocardiogram (ECG)) either in the ambulance or at a spoke centre 2. Diagnosis-Door PCI: time from diagnosis to arrival at the PCI centre 3. D2B: time from arrival at the PCI centre to balloon inflation (BI) and 4. Total ischemic time: time from SO to BI.

Patients were excluded if one of the following criteria was met: patients were walk-ins, they were not treated by PCI, D2B time was >180 minutes, system delay was unknown or mortality could not be retrieved.

pPCI procedure

The staff of the catheterization laboratory of the PCI centre was pre-informed about the estimated time of arrival of the patient and was activated well before the arrival of the

patient. In case the staff lived more than 30 minutes away from the PCI centre, they had to stay in the PCI centre while being on-call. All patients were treated pre-hospital with an intravenous bolus of 5000 IU of unfractionated heparin and 500 mg aspirin intravenously. During the study period the administration of clopidogrel on top of aspirin and heparin as pre-hospital treatment was implemented at July first 2006. The administration of GPIIBIIIA blockers in the pre-hospital phase was left at the discretion of the referring physicians.
The location of the acute vessel occlusion was determined in this study by the PCI operator. Consequently two groups were made according to the location: left anterior descending artery (LAD; anterior MI) versus non-LAD (non-anterior MI).

Statistical analysis

Statistical analysis was performed with SPSS 20.0. Continuous data were expressed as mean ± SD or median and interquartile range. Categorical data were presented as percentage. A Kruskal-Wallis test was used for continuous data, since they were non-Gaussian distributed. A Pearson's Chi-square test was used for categorical data. The continuous variable infarct size was converted into a dichotomous variable by dividing the de continuous variable in interquartile ranges and defining the interquartile range 0.75-1.00 as large enzymatic infarct size (75^{th} percentile). A p for trend was calculated for large enzymatic infarct size, and for 30-day and long term mortality between the quartiles of system delay.
To assess whether anterior MI might interfere with the relationship between system delay and 30-day and long term mortality, interaction testing was performed.
Logistic regression analyses was performed to estimate the effect of system delay on large enzymatic infarct size. Variables included in the models were age, gender, smoking, diabetes mellitus (DM), hypertension, hypercholesterolemia, previous MI, previous PCI, previous coronary artery bypass grafting (CABG), type of triage, ST deviation on diagnostic ECG and the quartiles of system delay. Cox regression analysis was performed to estimate the effect of system delay on 30-day and on long-term mortality. Variables included in the models for 30-day mortality were age, gender, DM, hypertension, type of triage, TIMI risk score and the quartiles of system delay. For the Cox regression analysis of long term mortality additionally previous MI, previous PCI and previous CABG were added.
All above described statistical tests were performed two-sided. In all statistical analyses p-values <0.05 were considered as statistically significant.
The study was conducted according to the principles of the Declaration of Helsinki and the protocol was approved by the local institutional review board. No extramural funding was used to support this work. The authors are fully responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

From 2005 until 2010, 4655 patients were referred to our hospital with the intention to perform pPCI. Three hundred twelve patients (7.7%) were walk-ins at the PCI-centre, 668

patients did not undergo PCI (14.3%), in 344 patients the D2B time was >180 minutes (7.4%), of 245 patients system delay was unknown (5.3%) and in 45 patients (1.0%) mortality could not be retrieved. Of the remaining 3041 patients, forty one percent (n=1253) of the patients had an anterior MI and 59% (n=1788) had a non-anterior MI. There was a significant interaction effect between anterior infarction and the quartiles of system delay on 30-day (p=0.048) and on long term mortality (p=0.027). Therefore, the results are presented separate for patients with an anterior MI and patients with a non-anterior MI.

Anterior MI

The baseline characteristics are described in Table 1. Patients with a prolonged system delay were older, were less often triaged in the field and had less ST-deviation on the diagnostic ECG. Gender, DM and the thrombolysis in myocardial infarction (TIMI) risk score differed among the quartiles of system delay. The time intervals are illustrated in Figure 1A. All time delays were significantly different between the quartiles of system delay. The median follow-up time was 5.3 (3.6-6.6) years. System delay was independently associated with a large enzymatic infarct size (Q2: OR 1.85 95% CI (1.19-2.86), Q3: OR 1.80 95% CI (1.15-2.81), Q4: OR 1.15 95% CI (0.72-1.84)). After Cox regression analysis prolonged system delay was independently associated with 30-day mortality (Q2: HR 1.18 95% CI (0.46-3.00), Q3: HR 2.45 95% CI (1.07-5.63), Q4: HR 2.25 95% CI (0.97-5.25)) and with long term mortality (Q2: HR 1.09 95% CI (0.71-1.68), Q3: HR 1.68 95% CI (1.13-2.49), Q4: HR 1.55 95% CI (1.03-2.33)) (Figure 2A).

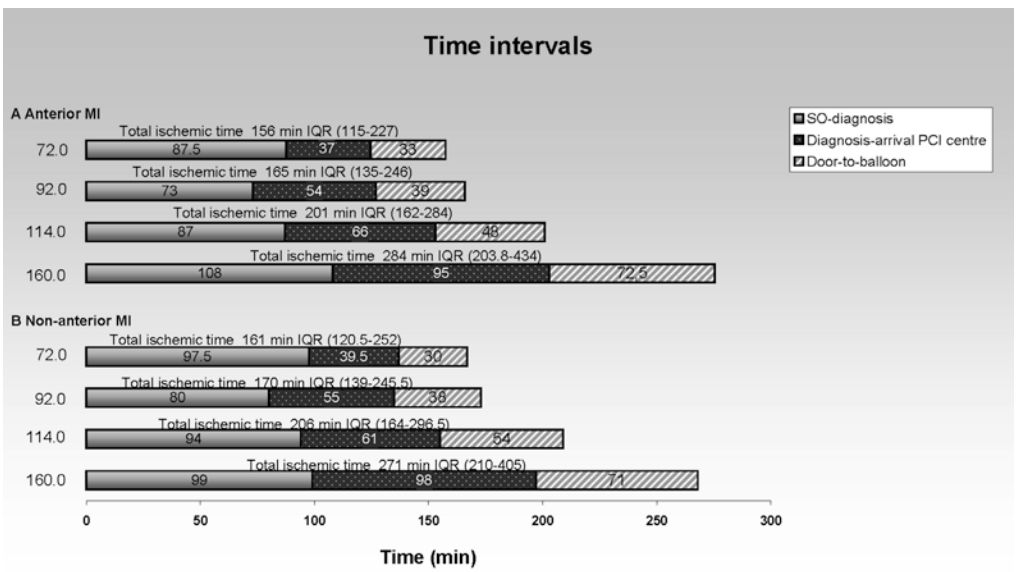
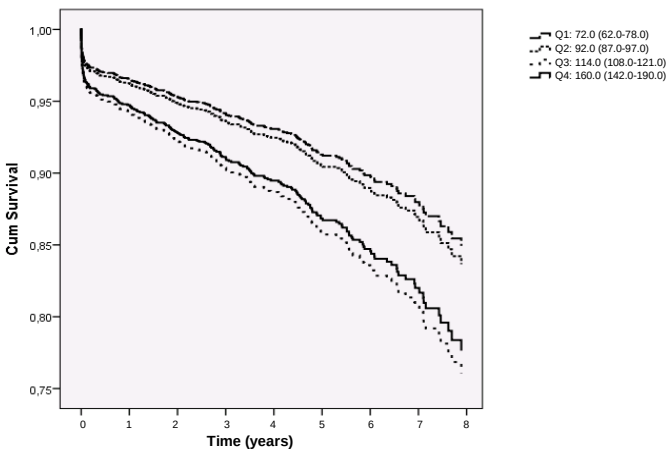


Figure 1. Time delays

The different time intervals are shown for patients with an anterior MI (A) and patients with a non-anterior MI (B). IQR: interquartile range, MI: myocardial infarction, min: minutes, PCI: percutaneous coronary intervention, SO: symptom onset.

Non-anterior MI

The baseline characteristics are described in Table 1. Patients with prolonged system delay more often had a previous CABG, were less often diagnosed in the field and had less ST-deviation on the diagnostic ECG. There was a difference in previous MI and TIMI risk score among the quartiles of system delay. The culprit vessel was in 1231 patients (68.8%) the right coronary artery (RCA) and in 425 patients (23.8%) the circumflex artery (CX). The time intervals are illustrated in Figure 1B. All time delays were significantly different between the quartiles of system delay. The median follow-up time was 5.2 (3.6-6.8) years. System delay was not associated with a large enzymatic infarct size (Table 2). After Cox regression analysis system delay was not associated with 30-day or with long term mortality (Figure 2B).



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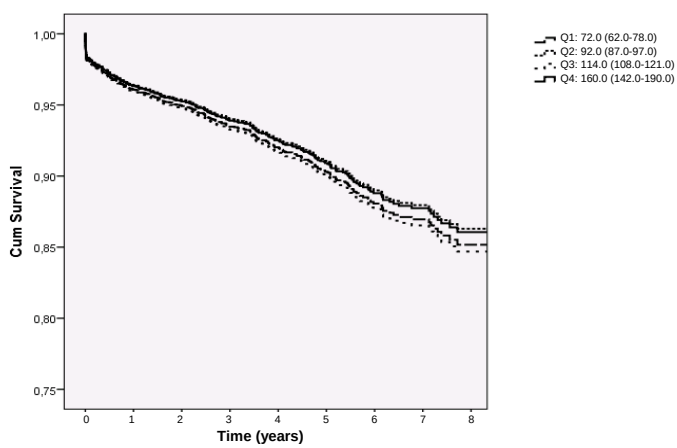

B

Figure 2. Mortality

Cox regression curves are shown for long term mortality for patients with an anterior MI (A) and patients with a non-anterior MI (B).

Table 1. Baseline characteristics

System delay in quartiles (min)	Q1: 72.0 (62.0-78.0)	Q2: 92.0 (87.0-97.0)	Q3: 114.0 (108.0-121.0)	Q4: 160.0 (142.0-190.0)	P
Characteristic					
Anterior MI	(n=313)	(n=321)	(n=323)	(n=296)	
Age years (mean ± SD)	62.6 ± 12.5 (n=313)	62.2 ± 12.7 (n=321)	65.8 ± 12.6 (n=323)	64.5 ± 13.2 (n=296)	0.001
Male gender	247/313 (78.9%)	241/321 (75.1%)	218/323 (67.5%)	218/296 (73.6%)	0.011
Previous MI	20/312 (6.4%)	27/321 (8.4%)	34/323 (10.5%)	32/296 (10.8%)	0.189
Previous CABG	3/313 (1.0%)	4/321 (1.2%)	6/323 (1.9%)	3/296 (1.0%)	0.734
Previous PCI	22/313 (7.0%)	24/321 (7.5%)	23/321 (7.2%)	32/296 (10.8%)	0.266
Hypertension	107/313 (34.2%)	88/320 (27.5%)	112/320 (35.0%)	108/295 (36.6%)	0.077
DM	25/313 (8.0%)	31/321 (9.7%)	50/323 (15.5%)	28/296 (9.5%)	0.012
Hypercholesterolemia	50/311 (16.1%)	53/319 (16.6%)	62/321 (19.3%)	67/294 (22.8%)	0.130
Smoking	124/312 (39.7%)	134/319 (42.0%)	111/317 (35.0%)	116/295 (39.3%)	0.332
Killip class >1	292/313 (93.3%)	299/321 (93.1%)	300/323 (92.9%)	265/294 (90.1%)	0.413
TIMI risk score (mean ± SD, median	3.24 ± 2.12	3.22 ± 2.07	3.56 ± 2.09	3.82 ± 2.30	<0.001
(IQR))	3.0 (1.0-4.0) (n=311)	3.0 (1.0-5.0) (n=321)	2.0 (3.0-5.0) (n=323)	4.0 (2.0-5.0) (n=294)	
Field triage	269/313 (85.9%)	239/321 (74.5%)	196/323 (60.7%)	134/296 (45.3%)	<0.001
GPIIBIIIA blocker*	82/263 (31.2%)	92/275 (33.5%)	99/283 (35.0%)	99/249 (39.8%)	0.217
ST segment deviation (diagnostic ECG)	13.48 ± 8.76	12.51 ± 7.87	12.51 ± 8.41	11.45 ± 10.53	0.001
	11.0 (8.0-17.0) (n=201)	11.0 (7.0-16.0) (n=216)	11.0 (7.0-16.0) (n=227)	8.0 (5.0-15.0) (n=220)	
Non-anterior MI	(n=462)	(n=429)	(n=448)	(n=449)	
Age years (mean ± SD)	62.5 ± 11.7 (n=462)	63.5 ± 12.2 (n=429)	63.1 ± 12.0 (n=448)	63.4 ± 12.1 (n=449)	0.488
Male gender	338/462 (73.2%)	323/429 (75.3%)	318/448 (71.0%)	327/449 (72.8%)	0.556
Previous MI	42/459 (9.2%)	41/427 (9.6%)	37/445 (8.3%)	64/448 (14.3%)	0.015
Previous CABG	10/461 (2.2%)	14/428 (3.3%)	16/447 (3.6%)	28/449 (6.2%)	0.012
Previous PCI	44/461 (9.5%)	44/428 (10.3%)	41/447 (9.2%)	52/447 (11.6%)	0.628
Hypertension	153/460 (33.3%)	137/427 (32.1%)	169/445 (38.0%)	176/446 (39.5%)	0.061
DM	52/461 (11.3%)	41/428 (9.6%)	53/444 (11.9%)	53/448 (11.8%)	0.669
Hypercholesterolemia	122/460 (26.5%)	84/425 (19.8%)	100/444 (22.5%)	111/446 (24.9%)	0.096

Smoking	208/455 (45.7%)	184/426 (43.2%)	210/440 (47.7%)	194/442 (43.9%)	0.536
Killip class >1	437/462 (94.6%)	399/428 (93.2%)	422/447 (94.4%)	423/448 (94.4%)	0.815
TIMI risk score (mean ± SD, median	2.17 ± 1.94	2.47 ± 2.09	2.45 ± 2.10	2.59 ± 2.02	0.008
(IQR))	2.0 (1.0-3.0) (n=459)	2.0 (1.0-4.0) (n=428)	2.0 (1.0-4.0) (n=446)	2.0 (1.0-4.0) (n=439)	
Field triage	397/462 (85.9%)	317/429 (73.9%)	287/448 (64.1%)	198/449 (44.1%)	<0.001
GPIIBIIIA blocker*	131/393 (33.3%)	120/385 (31.2%)	131/383 (34.2%)	118/381 (31.0%)	0.718
ST segment deviation (diagnostic ECG)	9.01 ± 6.21	8.50 ± 6.48	7.72 ± 6.25	6.34 ± 5.63	<0.001
	8.0 (5.0-11.0) (n=297)	7.0 (4.0-11.0) (n=279)	6.0 (4.0-10.0) (n=311)	5.0 (3.0-9.0) (n=303)	

* administered in the acute phase

BI: balloon inflation, CABG: coronary artery bypass graft, DM: Diabetes Mellitus, ECG: electrocardiogram, IQR: interquartile range, GPIIBIIIA: Glycoprotein IIBIIIA; MI: myocardial infarction, min: minutes, PCI: percutaneous coronary intervention, SD: standard deviation, TIMI: thrombolysis in myocardial infarction.

Table 2. Infarct size and mortality

System delay in quartiles (min)	Q1: 72.0 (62.0-78.0)	Q2: 92.0 (87.0-97.0)	Q3: 114.0 (108.0-121.0)	Q4: 160.0 (142.0-190.0)	P
Characteristic					
Anterior MI	(n=313)	(n=321)	(n=323)	(n=296)	
Infarct size (mean ± SD, IU/L n)*	2363.3 ± 2179.4	2712.3 ± 2415.3	2824.6 ± 2550.2	2594.7 ± 2814.4	P=0.141
	(n=306)	(n=313)	(n=317)	(n=288)	
Infarct size >75th percentile	107/306 (35.0%)	122/313 (39.0%)	130/317 (41.0%)	91/288 (31.6%)	P for trend =0.562
30 day mortality	8/313 (2.6%)	10/321 (3.1%)	22/323 (6.8%)	22/296 (7.4%)	P for trend =0.001
Long term mortality	40/313 (12.8%)	44/321 (13.7%)	78/323 (24.1%)	67/296 (22.6%)	P for trend <0.001
Non-anterior MI	(n=462)	(n=429)	(n=448)	(n=449)	
Infarct size (mean ± SD, IU/L, n)*	1662.9 ± 1640.4	1567.9 ± 1456.6	1670.0 ± 1558.6	1684.5 ± 1700.2	P=0.772
	(n=451)	(n=420)	(n=438)	(n=441)	
Infarct size >75th percentile	78/451 (17.3%)	65/420 (15.5%)	70/438 (16.0%)	82/441 (18.6%)	P for trend =0.590
30 day mortality	11/462 (2.4%)	13/429 (3.0%)	13/448 (2.9%)	13/449 (2.9%)	P for trend =0.676
Long term mortality	61/462 (13.2%)	64/429 (14.9%)	69/448 (15.4%)	73/449 (16.3%)	P for trend =0.195

* peak CK

MI: myocardial infarction, min: minutes, SD: standard deviation.

DISCUSSION

The present study is the first that assesses the effect of system delay on 30-day and long term mortality in anterior and non-anterior MI patients separately. Interestingly, our results demonstrate that in patients with an anterior MI system delay was significantly associated with 30-day and long term mortality. This effect was not apparent in patients with a non-anterior MI.

As demonstrated by Terkelsen et al. system delay seems to be the reasonable time delay to focus on in nonrandomized studies, since confounding, selection bias, information bias and recall bias hamper the other currently discussed time delays. Another advantage of this time delay is that this delay can be optimized during the pre-hospital triage as well as during the in-hospital triage [4].

Highly trained paramedics from several ambulance services transfer their patients to our high volume Isala hospital in which over 2000 PCIs are performed yearly. Even though all pre- and in hospital strategies and procedures are optimized, the variation between the quartiles of system delay differed between 72 min (Q1) versus ≥ 160 min (Q4). A possible explanation for the variation in system delay, is the fact that very sick patients are also included in this study and these patients have longer delays. As demonstrated, in general the TIMI risk score increases with system delay in both patient groups. Furthermore, D2B time increased with system delay despite an increase in patient delay (time from SO-diagnosis). The latter might be explained by the fact that in patients with the longest system delay (Q4) more often a decrease in symptoms was demonstrated after arrival in the PCI hospital. Non-system reasons might also account for these findings. Examples of non-system delays include delays in providing procedure consent, difficult access, difficulty crossing the culprit lesion and patients who have a cardiac arrest requiring intubation before PCI [11].

An increase in 30-day and long term mortality was demonstrated with system delay in patients with an anterior MI. We anticipated that in these patients also an increase in infarct size would be demonstrated since a large amount of myocardium is at risk in these patients and hence anterior MI is a strong baseline determinant of infarct size [12]. Furthermore, the association between system delay and infarct size has recently been demonstrated by Lønborg et al. and Tödt et al [13-14]. In our population however, only an increase in infarct size was demonstrated in patients with an anterior MI in the first three quartiles of system delay (Q1-Q3). An explanation for this result might be that patients with the longest system delays (Q4) had less severe and distinct symptoms and less deviations on the ECG, which has consequently lead to a prolonged D2B time. In addition, Lønborg et al. and Tödt et al. used magnetic resonance imaging to asses the myocardial area at risk, which was not used in our study.

While prolonged system delay is associated with an increased mortality, especially in patients with an anterior MI, it is of the greatest importance to minimize system delay as much as possible. Therefore, currently several strategies have been developed to reduce system delay and other time delays. Firstly, it is very important that the patients are triaged in the field by

an ambulance and are transferred straight to the cathlab of the PCI centre, bypassing the non-PCI centres and the emergency department of the PCI centre [15]. In our population the benefit of this implemented strategy was obvious, i.e. it was demonstrated that the amount of patients triaged in the field by an ambulance in Q1 was almost twice compared to the amount in Q4. Secondly, detailed identification of the time delays is essential so understanding can be gained. Thirdly, collaborative discussions and feedback to staff involved in the care of STEMI patients can make sure that the time delays can be optimized as much as possible. Points of discussion and feedback at present are 1) ECG recording by the highly trained paramedics in the ambulance, 2) central judgement of an ECG in the hospital, 3) timely preparation of cathlab and 4) pre- and in-hospital logistics [16].

Limitations

Firstly, the time of diagnosis was used together with the time of reperfusion therapy as a proxy for system delay. Information on the time of FMC was not available for all patients. However, a random sample of 94 cases revealed that in 83% of these patients the difference between FMC (i.e. EMS call) and diagnosis was ≤ 10 minutes. Secondly, since the project was not randomized and dispersed over several years, consequently the risk of unknown confounders exists. Thirdly, the level of peak CK within 24 hrs was used as surrogate parameter for infarct size.

CONCLUSIONS

Prolonged system delay significantly increased short as well as long term mortality in patients with an anterior MI. This effect was not demonstrated in patients with a non-anterior MI. Therefore it is of the greatest importance to minimize system delay in patients who present with an anterior MI.

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CHAPTER 6

EARLY AMBULANCE INITIATION VERSUS IN-HOSPITAL INITIATION OF HIGH DOSE CLOPIDOGREL IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

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ABSTRACT

BACKGROUND

Pre-hospital infarct diagnosis gives the opportunity to start anti-platelet and anti-thrombotic agents before arrival at the PCI centre. However, more evidence is necessary to demonstrate whether high dose (HD) clopidogrel (600 mg) administered in the ambulance is associated with improved initial patency of the infarct related vessel (IRV) and/or clinical outcome compared to in-hospital initiation of HD clopidogrel.

METHODS

From 2001 until 2009 all consecutive ST-Segment Elevation Myocardial Infarction (STEMI) patients who underwent pre-hospital diagnosis and therapy in the ambulance were prospectively included in our single-centre cohort study. We compared initial patency of the IRV and clinical outcome in patients treated from 2001 until June 2006 (in-hospital HD clopidogrel) with patients treated from July 2006 until 2009 (ambulance HD clopidogrel).

RESULTS

A total of 2475 patients with STEMI were registered; of these 1110 (44.8%) received in-hospital HD clopidogrel and 1365 (55.2%) received ambulance HD clopidogrel. Ambulance HD clopidogrel was not independently associated with initial patency (TIMI-2/3-flow pre-PCI (odds ratio: 1.18, 95% confidence interval [CI] 0.96–1.44); however, it was associated with fewer recurrent myocardial infarctions at 30 days (hazard ratio [HR]: 0.45, 95% CI 0.22–0.93) and at one year (HR: 0.45, 95% CI 0.25–0.80). No difference in TIMI 2/3 flow post-PCI, major bleeding, mortality, MACE – and the combination of mortality and recurrent myocardial infarction at 30-days and at one year was present between the two groups.

CONCLUSION

In conclusion, early in-ambulance as compared to in-hospital initiation of HD clopidogrel in STEMI patients did not improve initial patency of the IRV or clinical outcome, except for a reduction of recurrent myocardial infarction. Therefore, early administration of HD clopidogrel seems to have net clinical benefit for these patients.

INTRODUCTION

Early reperfusion is the primary goal of treatment for ST-Segment Elevation Myocardial Infarction (STEMI) patients. Primary percutaneous coronary intervention (PCI) is the recommended treatment for STEMI patients if it can be performed within 90 minutes (min) after first medical contact according to the American Heart Association/American College of Cardiology [1]. It is the preferred therapy according to the European Society of Cardiology if a primary PCI can be performed within 60 min or within 90 min if patients need to be transferred from a referral non-PCI centre to a PCI centre [2]. Furthermore, pre-treatment with anti-platelet and anti-thrombotic agents are important components of the medical treatment for these patients. Pre-hospital diagnosis in the ambulance with early administration of anti-platelet and anti-thrombotic agents before primary PCI gives the opportunity to start medical treatment directly after diagnosis [3-6]. Pre-treatment with a thienopyridine, like clopidogrel, on top of aspirin and heparin is common practice in many countries for STEMI patients undergoing primary PCI. However, more definitive evidence is necessary for this pre-treatment despite recommendation in the abovementioned guidelines [1-2]. Therefore, we have investigated in a large STEMI population whether high dose (HD) clopidogrel (600 mg) on top of aspirin and heparin administered in the ambulance (ambulance HD clopidogrel) is associated with improved initial patency of the infarct related vessel (IRV) and improved clinical outcome compared to in-hospital administration of HD clopidogrel (in-hospital HD clopidogrel).

MATERIALS AND METHODS

Since the early nineties STEMI patients were referred to the Isala hospital Zwolle and were treated by primary PCI. To improve the logistics of STEMI patients, the pre-hospital triage project was initiated. This has gradually been implemented in the region, starting in 1998. During the project all consecutive STEMI patients who were transported to our PCI centre from 1998 until 2009, were included in our cohort study prospectively. Criteria for the diagnosis of STEMI were: 1) history of cardiac symptoms of at least 30 min in the last 12 hours (h) or between 12 and 24 h if they had persistent symptoms with evidence of ongoing ischaemia prior to presentation at the PCI centre or referral non-PCI centre, 2) elevated levels of creatin kinase (CK) or CK-MB and 3) concurrent electrocardiogram changes: ST-segment elevation of >0.1 mV in at least two adjacent electrocardiogram leads [7]. Information on angiographic outcome and short- and long-term clinical outcome were registered.

Patients were excluded if they were referred via a referral non-PCI centre, were walk-ins at the PCI centre, if the type of pre-hospital triage was unknown, were admitted after an out of hospital cardiac arrest (OHCA) or were included in the Ongoing Tirofiban in Myocardial Infarction (On-TIME) 1 or 2 trial [8-9].

Procedures

The algorithm of pre-hospital triage has been described previously [10]. In brief: After patients dialled the emergency number, patients were triaged in the ambulance. If STEMI was suspected, an electrocardiogram was made by highly trained paramedics and a computerised algorithm revealed the diagnosis. If a diagnosis of STEMI was made, the ambulance went straight to the catheterisation laboratory of a PCI centre, bypassing the emergency departments of the referral non-PCI centre. All patients were treated with an intravenous bolus of 5,000 IU unfractionated heparin and 500 mg aspirin intravenously in the pre-hospital phase. From 2001 until June 2006 HD clopidogrel (600 mg orally) was administrated either upon arrival of the patient in the emergency room (ER), in the catheterisation room, during or after PCI. From July first 2006 onward all patients received HD clopidogrel on top of aspirin and heparin in the ambulance. The date of July first 2006 constitutes the dividing line, since at that moment the ambulance protocols were adapted: administration of HD clopidogrel was added to their protocols. All patients were treated with dual anti-platelet therapy for at least six months. In all patients in whom PCI was performed, the procedure was performed through femoral access. No patients received fibrinolytic therapy. The primary outcome of the study, initial patency defined as Thrombolysis in Myocardial Infarction (TIMI) 2/3 flow of the IRV, was recorded at initial angiography and was assessed by the executive cardiologist as previously reported [11]. The secondary outcomes of the study were TIMI 2/3 flow of the IRV post-PCI, major bleeding, recurrent myocardial infarction (MI), mortality, Major Adverse Cardiac Events (MACE) - and the combination of mortality and recurrent MI at 30 days and at one year. Major bleeding was defined and classified according to the TIMI criteria: intracranial bleeding or overt non-coronary artery bypass grafting (CABG)-related bleeding with a decrease in haemoglobin ≥5 g/dl (≥3.1 mmol/l) or a decrease in haematocrit ≥15% within 48 h after admission [12]. We used the following definition for recurrent MI: recurrent symptoms and/or new electrocardiographic changes in association with re-elevation of CK of >3 times the upper normal limit. More than five times the upper limit of normal CK was required for the diagnosis of MI after CABG. MACE was defined as mortality, recurrent MI and/or target vessel revascularisation.

Time intervals

Three different time intervals were evaluated: 1) Diagnosis-to-balloon time was defined as the time from diagnosis (time diagnostic electrocardiogram) to balloon inflation, 2) Door-to-balloon time was defined as the time from arrival PCI centre to balloon inflation and 3) Total ischaemic time was defined as the time from symptom onset to balloon inflation.

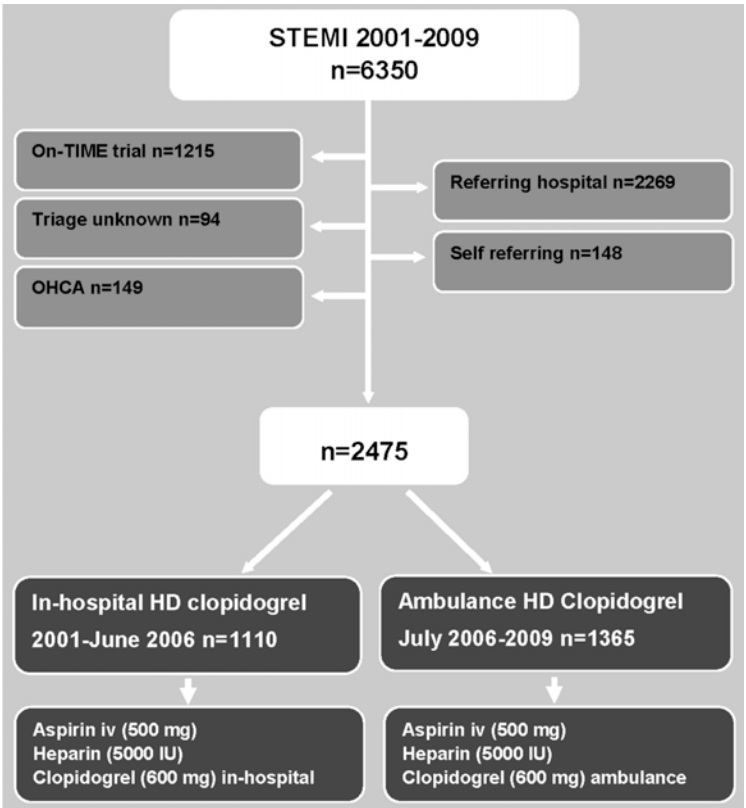

Figure 1. Study Flowchart

In total 6350 patients were transferred to our PCI centre. After excluding several patient groups 2475 patients were included in our study. Of these 2475 patients, 1110 patients received in-hospital HD clopidogrel and 1365 patients received HD clopidogrel in the ambulance.

HD: High Dose, OHCA: Out-of-Hospital Cardiac Arrest, On-TIME: Ongoing Tirofiban In Myocardial Infarction Evaluation, STEMI: ST-Segment Elevation Myocardial Infarction.

Statistical analysis

Statistical analysis was performed with SPSS 20.0 (Chicago, IL, USA). Continuous data were expressed as mean ± standard deviation or median and interquartile range. Categorical data were presented as percentage. A Mann-Whitney U test was used for comparing continuous data and Pearson's Chi-square test or Fisher's exact test was used for categorical data. Multivariable analyses were performed to estimate the effect of ambulance HD clopidogrel compared to in-hospital HD clopidogrel on TIMI 2/3 flow pre-PCI, on TIMI 2/3 flow post-PCI, on major bleeding, on MACE, and on the combination of mortality and recurrent MI at 30-days and at one year. Cox proportional-hazards regression models were used to estimate hazard ratios (HR) of recurrent MI - and mortality at 30 days and at one year. We corrected for the following baseline characteristics in the abovementioned analyses if they were defined as confounders: age, gender, diabetes mellitus, smoking, hypercholesterolemia, hypertension,

previous CABG, previous PCI, previous MI, Killip class >1, TIMI risk score, glycoprotein (GP)IIb/IIIa blocker administered in the acute phase, bailout GPIIb/IIIa blocker, total after ischaemic time, multivessel disease, thrombus aspiration, anterior infarction and stent choice. A landmark survival analysis was performed with the landmark time point chosen at 30 days the acute MI. The survival curves were compared by Log Rank test. To assess whether administration with GPIIb/IIIa blockers might interfere with the relationship between the type of clopidogrel treatment (in-hospital HD clopidogrel or ambulance HD clopidogrel) and TIMI 2/3 flow pre-PCI, interaction testing was performed. To assess whether administration with GPIIb/IIIa blockers (either in acute phase or as bail-out therapy) might interfere with the relationship between the type of clopidogrel treatment and recurrent MI at 30 days or at one year, interaction testing was performed. Furthermore, interaction testing was performed to assess whether the type of stent used (bare metal stent [BMS], drug-eluting stent [DES] or no stent implanted) might interfere with the relationship between the type of clopidogrel treatment and recurrent MI at 30 days or at one year. All described statistical tests were performed two-sided. In all statistical analyses p-values <0.05 were considered statistically significant.

The study was conducted according to the principles of the Declaration of Helsinki, and the protocol was approved by the local institutional review board. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

From 2001 until 2009, a total of 6350 patients were referred to the Isala hospital Zwolle with the intention to perform primary PCI. As shown in the patient flow chart in Figure 1, of these 2475 patients were referred after pre-hospital triage in the ambulance. Of these 2475 patients, a total of 1110 patients (44.8%) received inhospital HD clopidogrel and 1365 patients (55.2%) received HD clopidogrel in the ambulance. Patients treated with ambulance HD clopidogrel had a lower prevalence of smoking, they more often had a previous PCI, they were more often treated with GPIIb/IIIa blockers in the acute phase and pre- and/or post-PCI, they had shorter door-to-balloon times and in this patient group more often thrombus aspiration before PCI was performed (Table 1). Results on angiographic and clinical outcome are described in Table 2. Patients treated with ambulance HD clopidogrel more often had a TIMI 2/3 flow pre-PCI and - post-PCI and a lower incidence of recurrent MIs (Table 2). With a landmark survival analysis it was demonstrated that the difference in recurrent MIs between the groups could only be demonstrated in the first 30 days (Figure 2). No difference in major bleeding, mortality, MACE and the combination of mortality and recurrent MI at 30 days or at one year was demonstrated.

Table 1. Baseline clinical and angiographic characteristics

Characteristic	In-hospital HD clopidogrel n=1110	Ambulance HD clopidogrel n=1365	P
Age (mean ± SD)	63.2 ± 12.7 (n=1110)	64.1 ± 12.8 (n=1365)	0.130
Male gender	796/1110 (71.7%)	1017/1365 (74.5%)	0.118
Diabetes mellitus	132/1104 (12.0%)	157/1361 (11.5%)	0.747
Smoking	475/1069 (44.4%)	539/1355 (39.8%)	0.021
Hypercholesterolemia	229/1012 (22.6%)	279/1306 (21.4%)	0.465
Hypertension	374/1085 (34.5%)	490/1359 (36.1%)	0.415
Previous coronary artery bypass grafting	53/1109 (4.8%)	50/1362 (3.7%)	0.170
Previous PCI	92/1108 (8.3%)	149/1360 (11.0%)	0.027
Previous myocardial infarction	104/1108 (9.4%)	150/1358 (11.0%)	0.177
Killip class > 1	81/1100 (7.4%)	99/1365 (7.3%)	0.916
TIMI risk score (mean ± SD, median, IQR)	3.1 ± 2.2, 3.0 (1.0-4.0) (n= 304)	2.9 ± 2.2, 3.0 (1.0-4.0) (n= 1347)	0.318
GPIIb/IIIa blocker*	92/1110 (8.3%)	610/1365 (44.7%)	<0.001
Bail-out GPIIb/IIIa blocker	417/1110 (37.6%)	470/1365 (34.4%)	0.106
GPIIb/IIIa blocker pre- and/or post-PCI	496/1110 (44.7%)	929/1365 (68.1%)	<0.001
Diagnosis-to-balloon time (median, IQR)	-	99 (78.3-128) (n=960)	-
Door-to-balloon time (median, IQR)	55.0 (37.0-80.0) (n=943)	48.0 (31.0-75.0) (n=1093)	<0.001
Total ischemic time (median, IQR)	200.0 (145.0-298.8) (n=952)	191.0 (140.3-317.8) (n=1088)	0.683
Multivessel disease	558/1083 (51.5%)	653/1331 (49.1%)	0.229
Thrombus aspiration	2/276 (0.7%)	381/1348 (28.3%)	<0.001
Anterior myocardial infarction	452/1088 (41.5%)	574/1332 (43.1%)	0.443
Stent use:			0.174
- No stent	231/948 (24.4%)	358/1295 (27.6%)	
- BMS	537/948 (56.6%)	688/1295 (53.1%)	
- DES	180/948 (19.0%)	249/1295 (19.2%)	

* administered in the acute phase.

BMS: bare metal stent, DES: drug eluting stent, GP: glycoprotein, HD: High Dose, IQR: inter quartile range, PCI: Percutaneous Coronary Intervention, SD: standard deviation, TIMI: Thrombolysis In Myocardial Infarction

After multivariable adjustment, ambulance HD clopidogrel was not associated with TIMI 2/3 flow pre-PCI (odds ratio [OR]: 1.18, 95% confidence interval [CI] 0.96-1.44, TIMI 2/3 flow post-PCI, major bleeding mortality, MACE or the combination of mortality and recurrent MI at 30 day or one year. However, ambulance HD clopidogrel treatment was independently associated with less recurrent MIs at 30 days (HR: 0.45, 95% CI 0.22-0.93) and at one year (HR: 0.45, 95% CI 0.25-0.80) as compared to in-hospital HD clopidogrel treatment.

Table 2. Angiographic and clinical outcome

Characteristic	In-hospital HD clopidogrel n=1110	Ambulance HD clopidogrel n=1365	P
Angiographic outcome			
TIMI 2/3 flow pre-PCI	301/1015 (29.7%)	427/1149 (37.2%)	<0.001
TIMI 2/3 flow post-PCI	976/1012 (96.4%)	1125/1149 (97.9%)	0.038
Clinical outcome			
TIMI Major bleeding	16/1075 (1.5%)	11/1364 (0.8%)	0.110
30-day			
Mortality	35/1096 (3.2%)	46/1345 (3.4%)	0.756
MACE	58/1096 (5.3%)	68/1345 (5.1%)	0.793
Recurrent myocardial infarction	25/1096 (2.3%)	13/1345 (1.0%)	0.009
Mortality or recurrent myocardial infarction	57/1096 (5.2%)	57/1345 (4.2%)	0.262
1 year			
Mortality	60/1025 (5.9%)	79/1294 (6.1%)	0.800
MACE	98/1025 (9.6%)	123/1294 (9.5%)	0.964
Recurrent myocardial infarction	39/1025 (3.8%)	23/1294 (1.8%)	0.003
Mortality or recurrent myocardial infarction	96/1025 (9.4%)	100/1294 (7.7%)	0.159

HD: High Dose, MACE: Major Adverse Cardiac Event, PCI: Percutaneous Coronary Intervention, TIMI: Thrombolysis In Myocardial Infarction.

Results of subgroup analyses are demonstrated in Table 3. Patients treated with bail-out GPIIb/IIIa blockers and ambulance HD clopidogrel had a lower incidence of recurrent MIs at 30 days and at one year compared to patients treated with in-hospital HD clopidogrel. There was no significant interaction effect between the type of clopidogrel treatment and administration of GPIIb/IIIa blockers in the acute phase on TIMI 2/3 flow pre-PCI (p=0.269). There was no significant interaction effect between the type of clopidogrel treatment and administration of GPIIb/IIIa blockers (either in acute phase or as bail-out therapy) on recurrent MI at 30 days (p=0.912) or at one year (p=0.260). There was also no interaction effect between the type of clopidogrel treatment and type of stent used (BMS, DES or no stent implanted) on recurrent MI at 30 days (p=0.492) or at one year (p=0.288).

DISCUSSION

The most important finding of this study is that pre-hospital addition of HD clopidogrel on top of aspirin and heparin in the ambulance in STEMI patients did not improve initial patency of the IRV nor clinical outcome, except for a reduction of recurrent MI, as compared to patients treated with in-hospital initiation of HD clopidogrel. Our results can be explained by the fact that the peak effect of HD clopidogrel is time dependent [13-16].

Table 3. Subgroup analyses

	In-hospital HD clopidogrel	Ambulance HD clopidogrel	P
GPIIb/IIIa blocker (n=702)*			
TIMI 2/3 flow pre-PCI	27/80 (33.8%)	237/546 (43.4%)	0.102
Recurrent myocardial infarction at 30 days	1/90 (1.1%)	10/599 (1.7%)	0.694
Recurrent myocardial infarction at 1 year	1/83 (1.2%)	14/588 (2.4%)	0.497
Bail-out GPIIb/IIIa blocker (n=887)			
Recurrent myocardial infarction at 30 days	15/411 (3.6%)	3/463 (0.6%)	0.002
Recurrent myocardial infarction at 1 year	18/378 (4.8%)	8/442 (1.8%)	0.016
Thrombus aspiration (n=383)			
Recurrent myocardial infarction at 30 days	0/2	3/373 (0.8%)	1.000
Recurrent myocardial infarction at 1 year	-	6/369 (1.6%)	-

* administered in the acute phase.

GP: glycoprotein, HD: high dose, PCI: percutaneous coronary intervention, TIMI: Thrombolysis In Myocardial Infarction.

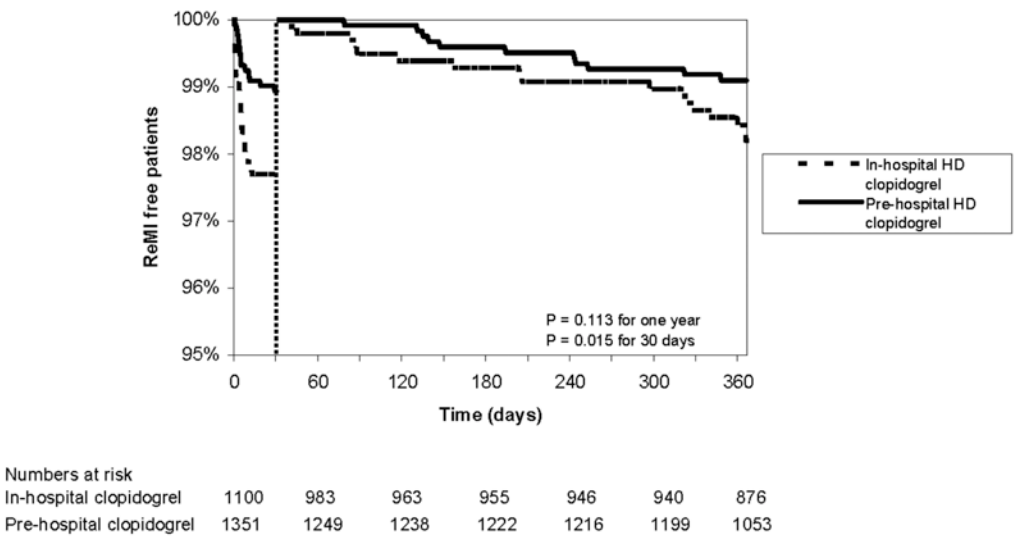

Figure 2. Recurrent myocardial infarction free patients

A landmark analysis of recurrent myocardial infarction free patients is performed for the patients treated with in-hospital HD clopidogrel (narrow black line) and treated with ambulance HD clopidogrel (black line).

In this study the clopidogrel preloading time was not sufficient to reach its peak of action and hence a lack of difference in IRV patency is the consequence. The second reason is that STEMI patients have an impaired bioavailability of clopidogrel, which results in suboptimal platelet inhibition [17]. The significant lower incidence of recurrent MI in patients treated with ambulance HD clopidogrel could only be demonstrated in the first 30 days. This might be due

to suboptimal platelet inhibition during the first 6-12 h after PCI especially in patients treated with in-hospital HD clopidogrel. Patients treated with HD clopidogrel in the ambulance had a pre-loading time of approximately 100 min, since the surrogate time interval (time from diagnosis to balloon inflation) was 99 (78.3-128) min, whereas the timing of administration of clopidogrel in the period before July first 2006 was later and not strict: 20% of the patients received the loading dose in the catheterisation laboratory, although the majority of the patients were treated after PCI was performed, most often in the cardiac care department. This relatively late administration in the latter patients might have put them at increased risk of recurrent MI. Furthermore, we anticipate that early clopidogrel administration might have had a protective effect on acute stent thrombosis and therefore the incidence of recurrent MIs decreased with ambulance HD clopidogrel. However, stent thrombosis was not prospectively collected in our database, and therefore this explanation should be read with cautiousness. As demonstrated in other STEMI trials, ambulance HD clopidogrel was not associated with an increased bleeding risk in these patients [18-22]. In the ACCOAST trial, however, an increase in TIMI major bleeding was demonstrated in patients assigned to inhospital pretreatment with prasugrel compared to placebo [23]. There were several trials which support our results [20-21, 24]. Dörler et al. demonstrated that pre-treatment with clopidogrel did not improve initial patency of the IRV and reduced the incidence of recurrent MIs. However, they also showed that clopidogrel pre-treatment led to a reduced in-hospital mortality and stroke, which was not demonstrated in our study [20]. In the randomised controlled trial of Zeymer et al. (n=337), they have demonstrated that pre-hospital clopidogrel did not improve initial TIMI 2/3 flow pre-PCI and ST-resolution 1 h post-PCI. However, this study was stopped prematurely [21]. Ducci et al. demonstrated in their small randomised trial (n=168) also no difference between pre- (900 or 600 mg) versus in-hospital (300 mg) administration of clopidogrel on TIMI 2/3 flow pre-PCI [24]. There were also trials who did not support our results on the TIMI 2/3 flow pre-PCI [18, 25-26]. Fever et al. and Lev et al. showed that pre-treatment with clopidogrel reduced a composite endpoint of recurrent acute coronary syndrome, congestive heart failure, stent thrombosis and 30-day mortality [18], improved initial TIMI flow and reduced the incidence of recurrent MI [26]. A shortcoming in these two trials is the small sample size, which underpowered the studies to assess the effect of clopidogrel pre-treatment on mortality. Vlaar et al. demonstrated that pre-treatment with clopidogrel improved TIMI 2/3 flow pre-PCI and decreased mortality as well as the composite endpoint (mortality and MI). It is of importance to note that in the analysis of Vlaar et al. studies with different trial designs, pharmacologic therapies and PCI strategies during and after PCI were included [25]. In the large observational study of Koul et al. they demonstrated that clopidogrel treatment prior to arrival at the cathlab was associated with a reduction in the combined risk of mortality or MI as well as mortality alone in STEMI patients undergoing pPCI. However, they did not demonstrate a significant reduction in MI at one year, since after propensity scoring or multivariable analysis on top of propensity scoring the significant reduction in MI disappeared. Although, they stated that the general tendency in

almost all trials is a reduction in MI with pre-treatment of clopidogrel. Unfortunately, the effect on initial patency was not examined. Furthermore, the clopidogrel loading dose was not specified to 300 or 600 mg and it was unknown whether all patients in the control group received clopidogrel in-hospital [22]. To improve initial patency of the IRV and clinical outcome in STEMI patients undergoing primary PCI, the results of pre-treatment with the GPIIb/IIIa blocker tirofiban, on top of aspirin, heparin and clopidogrel have been demonstrated [27]. The effect of tirofiban was time-dependent, whereas the time-dependent effect on initial patency was not found in the control group pre-treated with HD clopidogrel only [28]. As expected in our study, the difference in recurrent MI was not demonstrated in the patients who were treated with a GPIIb/IIIA blocker in the acute phase. Therefore, administration of a GPIIb/IIIa blocker seems to have a protective effect on recurrent MI. Recently, several trials have been initiated to assess the efficacy of pre-treatment in the ambulance with new agents, like ticagrelor (ATLANTIC trial, EudraCT number: 2011-000214-19), which are characterised with an earlier peak of effects. However, it remains speculative whether the administration of an oral as compared to an intravenous agent is equally effective in patients with acute MI. Therefore, it might be very interesting to investigate the pre-treatment effect of the intravenous agent cangrelor in the near future, because of its fast-acting and rapidly reversible parenteral onset [29].

Limitations

The exact time of administration of the HD clopidogrel was not collected prospectively, so it is impossible to assess the real loading dose-to-balloon time. This limitation is the consequence of the fact that our analyses are retrospective analyses from a prospective data registry. Since the project was not randomised and was dispersed over several years, consequently the risk of unknown confounders exists. The lack of randomisation might have led to selection bias. We decided that it was not appropriate to correct for selection bias by performing a propensity score matching procedure while concealed sources of bias ambush and therefore could lead to overestimation of the examined effect. The only known concealed source of bias in our study is the moment of admission at the PCI centre. The patients in this study were classified into the group ambulance HD clopidogrel or in-hospital HD clopidogrel based on the year and month of admission: on July first 2006 there was a protocol adaptation in the ambulances and from that time patients were treated with ambulance HD clopidogrel. Moreover, there are some confounders that were not present in the first years of the study. For example several study patients were pre-treated with GPIIb/IIIa blockers before primary PCI which occurred for the first time in 2005. Therefore, propensity score matching does not seems to be appropriate. The protocol adaptation in the ambulances on July 1, 2006 with HD clopidogrel administration coincided with an increase in pre-treatment with GPIIb/IIIa blockers before primary PCI and an increase in initiation of thrombus aspiration. Therefore, our results could reflect these effects rather than demonstrating the effect of ambulance HD clopidogrel alone. Interaction testing was not applicable for the effect of thrombus aspiration,

because of the very few numbers of patients treated with in-hospital HD clopidogrel. However, adjustment for both variables was taken into account in the regression models. Currently, clopidogrel is no longer the P2Y12 blocker of choice as peri-procedural pharmacotherapy according to the guidelines [1-2]. Ticagrelor (ATLANTIC trial) and prasugrel should be suggested first, before considering clopidogrel administration. We are aware of the fact that the ischaemic time and door-to-balloon time in our study are relatively short and that our results can not be applied to STEMI patients with long ischaemic and long door-to-balloon times.

Conclusion

Early in-ambulance as compared to in-hospital initiation of HD Clopidogrel in STEMI patients did not improve initial patency of the IRV or clinical outcome, except for a reduction of recurrent MI. Therefore, early administration of HD clopidogrel seems to have net clinical benefit for these patients, who were included in a prospective cohort study and in which GPIIb/IIIa blocker administration in the acute phase increased during the years.

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PART II PREDICTORS FOR STEMI PATIENTS AT RISK

CHAPTER 7

PREDICTORS AND OUCTOME OF GRADE 3 ISCHEMIA IN PATIENTS WITH ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION UNDERGOING PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

PURPOSE

Grade 3 ischemia (G3I: distortion of the terminal portion of the QRS complex) is a predictor of serious complications after acute myocardial infarction. However, less is known about which patients are more prone to present with G3I.

METHODS

Patients who were enrolled in the Ongoing Tirofiban In Myocardial infarction Evaluation trial 2 were included. These patients were divided in 2 groups based on the enrolment electrocardiogram: grade 2 ischemia (G2I) or G3I.

RESULTS

Between June 2004 and November 2007, 1308 patients with interpretable electrocardiograms were enrolled. Grade 3 ischemia was found in 426 (32.6%) patients. Patients with G3I were older, more often male, more often had diabetes, had a Thrombolysis In Myocardial Infarction (TIMI) risk score of greater than 3, had 3 vessel disease, had an anterior infarction, more often presented in Killip class greater than 1, less often had a pre-procedural TIMI 3 flow, and less often had a myocardial blush grade 3 post-PCI. One hour post-PCI, residual ST deviation was higher in patients with G3I compared with patients with G2I. Furthermore, G3I was associated with more major cardiac events (including death, myocardial infarction, urgent target vessel revascularization). After multivariate adjustment, G3I was an independent predictor of failure of ST-segment resolution 1 hour post-PCI (odds ratio, 1.4; 95% confidence interval, 1.1-1.9) and 30-day mortality (odds ratio, 3.2; 95% confidence interval, 1.2-8.7).

CONCLUSION

Grade 3 ischemia was associated with high-risk patient criteria (older age, diabetes, TIMI risk score N3, Killip class N1, and anterior myocardial infarction) and represents a subgroup of high-risk patients who seems to be associated with poor myocardial reperfusion and worse outcome.

INTRODUCTION

Primary percutaneous coronary intervention (pPCI) is a highly effective therapy to reestablish myocardial flow in patients with an ST-segment elevation myocardial infarction (STEMI). After pPCI, Thrombolysis In Myocardial Infarction (TIMI) 3 flow can be achieved in 85% to 95% of the patients; however, the prognosis of STEMI patients is highly dependent on the restoration of adequate perfusion at the level of the microcirculation [1-2]. Beyond the infarct related artery flow, ST-segment resolution (STR) seems to be an even stronger marker to identify tissue reperfusion [3-6]. In STEMI, incomplete STR (b70%) or failure of STR after reperfusion therapy is associated with worse outcome [4-5, 7-9].

Because early risk stratification for STEMI patients is crucial, numerous investigators have determined Electrocardiographic parameters to predict successful reperfusion in STEMI patients at admission [10-15]. One of these parameters is distortion of the terminal portion of the QRS complex (grade 3 ischemia [G3I]) described by Sclarovsky et al [16] and Birnbaum et al. [13]. This parameter has been identified as an independent predictor of failure of STR for STEMI patients who received reperfusion therapy and is associated with worse outcome [13, 16-21]. However, less is known about which patients are more prone to present with G3I, and therefore, we investigated this topic in a large population.

METHODS

Study population

The Ongoing Tirofiban in Myocardial Evaluation (On-TIME) 2 trial was a prospective, multicenter, placebo-controlled, randomized clinical trial. The study consisted of 2 phases: (1) an open-label run-in phase and (2) a placebo-controlled double-blind phase. The rationale, study design, and primary results of the On-TIME 2 trial have been described previously [22-23]. Patients with STEMI who underwent pPCI were included. Eligible patients were men and women aged between 21 and 85 years with symptoms of an acute myocardial infarction (MI) of more than 30 minutes but less than 24 hours and presented with ST-segment elevation (>0.1 mV in 2 adjacent Electrocardiographic [ECG] leads). Exclusion criteria were therapy-resistant cardiogenic shock, renal dysfunction, persistent severe hypertension, contraindication to anticoagulation, increased bleeding risk, pregnancy or breastfeeding, life expectancy of less than 1 year, and left bundle-branch block.

Written informed consent was obtained by an intensive care nurse in the ambulance or by a physician in a referral hospital. All local ethical committees involved approved the study protocol of the On-TIME 2 trial.

Electrocardiographic analysis

All interpretable and available ECGs of the On-TIME 2 patients were analyzed by 1 employee of an independent ECG core laboratory (Diagram BV, Zwolle, The Netherlands) who had no knowledge of the patients' angiographic or clinical outcome. In case of doubt, a second core-laboratory employee reevaluated the ECG, and consensus was reached in all cases. ST-

segment elevation was measured at the J point in each lead, except aVR. STR was defined as the percent difference between the sum of ST-segment elevation at the diagnosis ECG and the sum of ST-segment elevation at the ECG pre-PCI (STR pre-PCI) or the ECG 1 hour post-PCI (STR post-PCI). Complete STR was defined as 70% or greater resolution [24-25]. The sum of ST-segment deviation was measured 20 milliseconds after the end of the QRS complex compared to the isoelectric line with a caliper (diagnostic, pre-PCI, and 1 hour post-PCI). The grade of ischemia was analyzed at the diagnostic ECG and defined according to the ischemia grading system of Birnbaum et al [13]. Grade 3 ischemia was defined as (1) absence of an S wave below the TP-PR isoelectric line in 2 or more leads that usually have a terminal S configuration (leads V1-V3) or (2) ST J point amplitude of 50% or greater of the R-wave amplitude measured from the TP-PR baseline in 2 or more all other infarct-related leads (Figure 1).

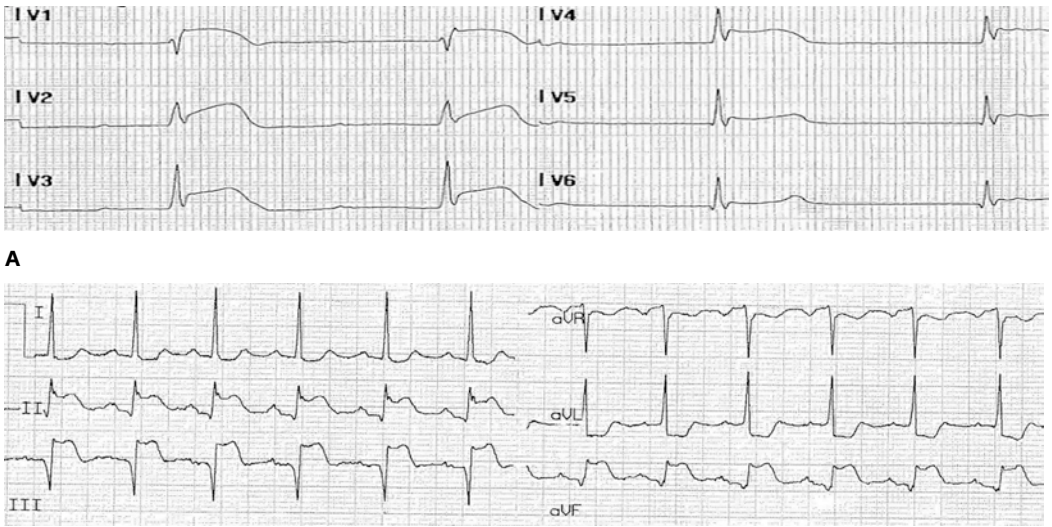
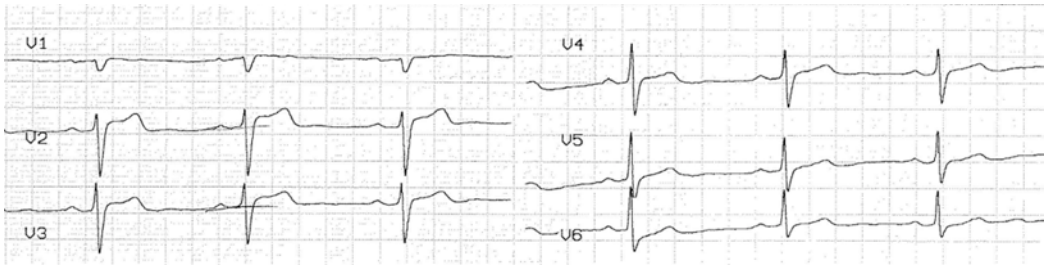
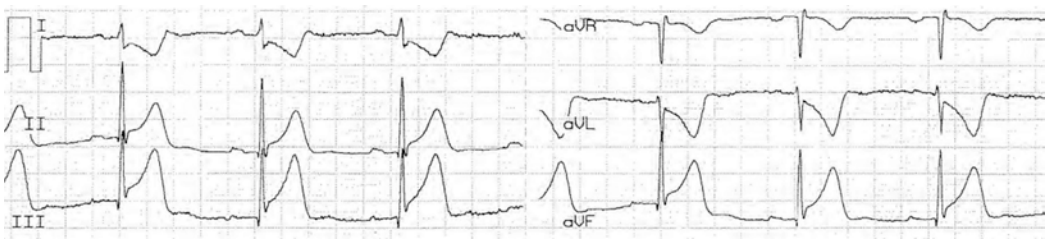


Figure 1.
Diagnostic ECG of a patient with anterior ST-segment elevated myocardial infarction (STEMI) (A) and an inferior STEMI (B) showing grade 3 ischemia. There is ST-elevation in lead V1-V6 and there are no S waves in V2-V3 (A). There is ST-elevation in II, III and aVF and the ST J-point amplitude is ≥50% of the R wave amplitude in these leads (B).

Patients meeting the ST-segment elevation criteria but not the aforementioned G3I criteria were defined as grade 2 ischemia (G2I) (Figure 2). Patients were excluded if the ST deviations were not fulfilling the study criteria. Furthermore, negative T waves were not considered for inclusion.



A



B

Figure 2.

Diagnostic ECG of a patient with an anterior STEMI (A) and an inferior STEMI (B) showing grade 2 ischemia. There is ST-elevation in V2-V4, however S waves are present in V1-V3 (A). There is ST-elevation in lead II, III and aVF, however the J-point amplitude is below the 50% of the R wave amplitude (B).

Angiographic analysis

Coronary angiography and PCI were performed according to each institution's guidelines and standards. The angiograms were analyzed by an independent core laboratory (Diagram BV) without knowledge of the patient's electrographic or clinical outcome. The TIMI flow grade was assessed pre- and post-PCI, and myocardial blush grade (MBG) was assessed post-PCI as previously described [26-27]. Distal embolization and thrombus burden were defined as previously described [28-29].

Clinical end points

The primary end point of the On-TIME2 trial was residual ST-segment deviation at 1 hour after PCI, as previously described [7,24]. The key secondary end point was major adverse cardiac events (death, recurrent MI, and target vessel revascularization [TVR]) at 30 days. Infarct size, which was one of the other end points, was calculated as the peak level of creatine kinase (CK) (peak CK) within 48 hours after admission [25]. A blinded independent clinical end-point committee adjudicated all clinical end points.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 (Chicago, Illinois). Continuous data were expressed as mean ± SD or median and interquartile range. Categorical data were presented as percentage. Analysis of variance was used for continuous data, and Pearson ☐2 test was used for the categorical data, respectively. For categorical data with a linear trend, a linear-

by-linear association test was used. We tested the associations between the variable “G3I” and other baseline characteristics using univariate logistic regression. The Mann-Whitney U test was used to calculate the time intervals between the G3I group and the G2I group because these were non-Gaussian distributed. To assess independent predictors of G3I, multivariate analysis was performed using a logistic regression analysis. In this analysis, univariate variables with P <0.10 were included. In all the statistical analyses, P ≤ 0.05 was considered statistically significant.

RESULTS

Between June 2004 and November 2007, 1385 patients were included in the On-TIME 2 trial. Twenty-nine patients (2.1%) were excluded because of incomplete or uninterpretable ECGs, and 48 patients (3.5%) were excluded because of ST deviations not fulfilling the study criteria. From the remaining 1308 patients, G3I was found in 426 patients (32.6%). Table 1 summarizes the baseline characteristics of the patients. Patients with G3I were older, more often male, more often had diabetes, had a TIMI risk score of greater than 3, more often had triple vessel disease, had an anterior infarction, more often presented in Killip class greater than 1, less often had a preprocedural TIMI 3 flow, and less often had an MBG 3 post-PCI (Tables 1 and 2). Furthermore, these patients had a longer time from symptom onset (SO) to diagnosis and a prolonged ischemic time (Figure 3).

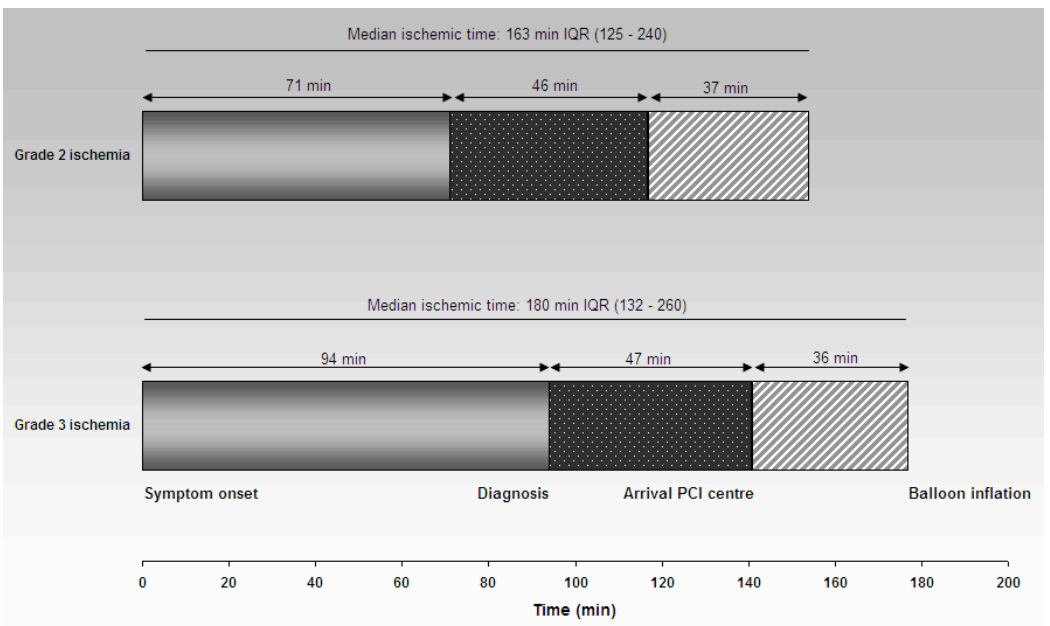


Figure 3.

The different time intervals are shown for patients with grade 2 ischemia and grade 3.

Table 1. Baseline characteristics

Characteristic	Total (N = 1308)	Grade 2 ischemia (N = 882)	Grade 3 ischemia (N = 426)	P
Age ± SD	61.69 ± 11.87	60.89 ± 11.81	63.33 ± 11.83	<0.001
Male gender	996/1308 (76.1%)	657/882 (74.5%)	339/426 (79.6%)	0.043
Hypertension	425/1304 (32.6%)	280/879 (31.9%)	145/425 (34.1%)	0.414
Diabetes	144/1304 (11.0%)	84/879 (9.6%)	60/425 (14.1%)	0.014
Smoking	612/1287 (47.6%)	420/868 (48.4%)	192/419 (45.8%)	0.388
Hypercholesterolemia	322/1300 (24.8%)	209/877 (23.8%)	113/423 (26.7%)	0.259
Family history	517/1276 (40.5%)	361/862 (41.9%)	156/414 (37.7%)	0.153
Previous Angina	225/1301 (17.3%)	152/880 (17.3%)	73/421 (17.3%)	0.976
Previous MI	109/1303 (8,4%)	67/879 (7.6%)	42/424 (9.9%)	0.163
Previous PCI	100/1306 (7.7%)	64/881 (7.3%)	36/425 (8.5%)	0.442
Previous CABG	24/1306 (1.8%)	19/881 (2.2%)	5/425 (1.2%)	0.217
Previous CVA	20/1305 (1.5%)	15/880 (1.7%)	5/425 (1.2%)	0.467
TIMI risk score >3	378/1290 (29.3%)	211/871 (24.2%)	167/419 (39.9%)	<0.001
Killip class >1	150/1280 (11.7%)	89/863 (10.3%)	61/417 (14.6%)	0.024
Anterior MI	525/1228 (42.8%)	285/828 (34.4%)	240/400 (60%)	<0.001
Vessel disease				
One	659/1296 (50.8%)	462/872 (53.0%)	197/424 (46.5%)	0.028
Two	354/1296 (27.3%)	228/872 (26.1%)	126/424 (29.7%)	0.176
Three	219/1296 (16.9%)	131/872 (15.0%)	88/424 (20.8%)	0.010
Left main	14/1296 (1.1%)	7/872 (0.8%)	7/424 (1.7%)	0.250
IRV				
LAD	511/1235 (41.4%)	267/822 (32.5%)	244/413 (59.1%)	<0.001
RCA	559/1235 (45.3%)	430/822 (52.3%)	129/413 (31.2%)	<0.001
CX	149/1235 (12.1%)	115/822 (14.0%)	34/413 (8.2%)	0.003
Graft	10/1235 (0.8%)	8/822 (1.0%)	2/413 (0.5%)	0.510
LM	6/1235 (0.5%)	2/822 (0.2%)	4/413 (1.0%)	0.101
Cum ST segment deviation*	14.65 ± 8.77	13.08 ± 7.08	17.90 ± 10.82	<0.001

*Determined at the diagnostic ECG.

CABG: coronary artery bypass grafting, CVA: cerebro vascular accident, Cum: cumulative, CX: circumflex, IRV: infarct related vessel, LAD: left anterior descending, LM: left main, MI: myocardial infarction, PCI: percutaneous coronary intervention, RCA: right coronary artery, SD: standard deviation, TIMI: thrombolysis in myocardial infarction.

Table 2. Angiographic, enzymatic, electrographic and clinical outcome

Characteristic	Grade 2 ischemia (N = 882)	Grade 3 ischemia (N = 426)	P
Angiographic and enzymatic outcome			
TIMI 3 flow pre-PCI	187/803 (23.3%)	55/406 (13.5%)	<0.001
TIMI 3 flow post-PCI	690/760 (90.8%)	344/389 (88.4%)	0.208
MBG 3 post-PCI	329/718 (45.8%)	145/368 (39.4%)	0.043
Infarct size ± SD *(IU/l, N=1269)	1499 ± 1473	2295 ± 2059	<0.001
Stent placement	680/767 (88.7%)	359/392 (91.6%)	0.122
BMS	509/679 (75.0%)	271/359 (75.5%)	0.853
DES	181/679 (26.7%)	92/359 (25.6%)	0.720
Additional devices	118/845 (14.0%)	84/416 (20.2%)	0.005
Rescue thrombosuction	81/845 (9.6%)	50/416 (12.0%)	0.183
IABP	27/845 (3.2%)	31/416 (7.5%)	<0.001
Collaterals			0.245
0	394/633 (62.2%)	231/340 (67.9%)	
1	165/633 (26.1%)	81/340 (23.8%)	
2	55/633 (8.7%)	20/340 (5.9%)	
3	19/633 (3.0%)	8/340 (2.4%)	
Distal embolisation pre-PCI	23/299 (7.7%)	5/109 (4.6%)	0.272
Thrombus burden			0.003
0	19/788 (2.4%)	6/395 (1.5%)	
1	49/788 (6.2%)	16/395 (4.1%)	
2	32/788 (4.1%)	12/395 (3.0%)	
3	139/788 (17.6%)	61/395 (15.4%)	
4	178/788 (22.6%)	79/395 (20.0%)	
5	371/788 (47.1%)	221/395 (55.9%)	
Electrographic outcome			
Com ST resolution pre-PCI	147/746 (19.7%)	34/338 (10.1%)	<0.001
Res ST deviation pre-PCI	10.55 ± 8.53	15.33 ± 10.35	<0.001
Res ST deviation 1 hr post-PCI			
Mean (mm, N=1211)	3.60 ± 5.45	5.37 ± 5.71	<0.001
0 mm	315/825 (38.2%)	79/386 (20.5%)	<0.001
1-3 mm	222/825 (26.9%)	91/386 (23.6%)	
4-6 mm	142/825 (17.2%)	97/386 (25.1%)	
>6 mm	146/825 (17.7%)	119/386 (30.8%)	
Res ST deviation >3 mm 1 hr post-PCI	288/825 (34.9%)	216/386 (56.0%)	<0.001
Com ST resolution 1 hr post-PCI	538/814 (66.1%)	214/381 (56.2%)	<0.001
Clinical outcome			
30-day			
Stroke	7/852 (0.8%)	2/408 (0.5%)	0.726
MI	17/852 (2.0%)	10/408 (2.5%)	0.601
Urgent TVR	28/852 (3.3%)	23/408 (5.6%)	0.048
Death, MI, urgent TVR (MACE)	49/852 (5.8%)	43/408 (10.5%)	0.002
Mortality	18/852 (2.1%)	21/408 (5.1%)	0.004
1-year			
MI	21/846 (2.5%)	15/402 (3.7%)	0.218
Mortality	31/846 (3.7%)	28/402 (7.0%)	0.010

*peak CK

BMS: bare metal stent, Com: complete, CK: creatine kinase, DES: drug eluting stent, IABP: intra aortic balloon pump, MACE: major adverse cardiac event, MBG: myocardial blush grade, MI: myocardial infarction, PCI: percutaneous coronary intervention, Res: residual, TIMI: thrombolysis in myocardial infarction, TVR: target vessel revascularization.

Cumulative ST-segment deviation at the diagnostic ECG was higher for patients with G3I. One hour after PCI, residual ST-segment deviation and residual ST-segment deviation greater than 3 mm post-PCI was higher in G3I patients. Furthermore, complete STR (STR pre-PCI and STR post-PCI) was lower in patients with G3I compared to G2I patients (Table 2).

Moreover, G3I was associated with a larger infarct size, a higher 30-day mortality, a higher 1-year mortality, more urgent TVRs at 30 days, and more major cardiac events (including death, MI, urgent TVR) (Table 2). After multivariate adjustment, G3I was an independent predictor of failure of STR post-PCI (odds ratio, 1.4; 95% confidence interval, 1.1-1.9) and 30-day mortality (odds ratio, 3.2; 95% confidence interval, 1.2-8.7).

DISCUSSION

The primary finding of this study is that STEMI patients with a higher age, male sex, a TIMI risk score greater than 3, Killip class greater than 1, and anterior MI were more prone to present with G3I compared with G2I. Furthermore, G3I was identified as an independent predictor of failure of STR post-PCI and 30-day mortality.

Careful risk assessment for each patient contributes to the decision making of physicians regarding therapeutic interventions, triage among alternative levels of hospital care, and allocation of clinical resources. Therefore, several electrocardiographic parameters have been identified as guiding management [10-15]. The parameter G3I has been demonstrated to be an independent predictor of failure of STR post-PCI and mortality for patients treated with thrombolytic therapy as well as for patients treated with pPCI [13, 16-21]. These results are consistent with our findings. Only baseline characteristics were included in the multivariate analyses because these data were present at the time of risk assessment. If we would have included angiographic parameters, the clinical predicting power would be reduced.

To identify high-risk STEMI patients early after SO, we have demonstrated in the present study which characteristics and therefore which patients are more prone to present with G3I. Previous studies showed that a higher age [13, 20-21, 30], diabetes [13], and large infarct size were predictors of G3I [13, 17, 21, 30-31]. A TIMI risk score of greater than 3 has not been identified earlier as characteristics of G3I. In contrast to a previous study, more patients in our population with G3I were men [31]. However, we do not have a proper explanation for this significant difference. Some [13, 21] but not all [14, 17, 32-33], prior studies have shown a higher prevalence of Killip class greater than 1. We have demonstrated a higher prevalence of anterior STEMIs [17, 30] in contrast to other studies [13-14, 21, 32]. A possible explanation for the higher prevalence might be that these anterior wall infarctions lead generally to larger infarct sizes that result in more tissue and microcirculatory damage and microvascular dysfunction [31]. Reduced TIMI 3 flow pre-PCI has also been described previously [31], whereas others showed reduced TIMI 3 flow post-PCI [19], no reflow post-PCI [34, 35], or no association between G3I and TIMI flow at all [32]. Absence of MBG 3 post-PCI has not prior been identified as consequence of G3I. Weaver et al [31] recently demonstrated no significant difference in MBG 3 post-PCI between G2I and G3I patients

nevertheless, the sample size of their study was very small. Residual ST-segment deviation post-PCI was also higher in patients with G3I, which was also demonstrated by Birnbaum et al [21]. Furthermore, we found a prolonged time from SO to diagnosis and a prolonged ischemic time in patients with G3I in contrast to previous studies [13-14, 21].

The aforementioned data reveal that patients with G3I not only have less successful restoration of the blood flow in the epicardial coronary arteries but also have less successful reperfusion in the infarcted myocardium. Consequently, patients with G2I have a better protection of the myocardium and have less severe ischemia. The combination of aforementioned characteristics of patients with G3I might explain their worse outcome however, the reason why the extent and the grade of ischemia are related to worse outcome remains speculative.

To improve treatment for patients with G3I, the simple electrographic measurement, available at the diagnostic ECG, should perhaps be implemented in routine practice (ie, implementation in protocols for STEMI patients). This might lead to a reduced diagnosis-to-door PCI time and more often to direct transport by ambulance to the catheterization laboratory of a PCI center, bypassing the emergency departments of non-PCI spoke centers.

CONCLUSION

Grade 3 ischemia, which may be diagnosed on the initial diagnostic ECG, was associated with high-risk patient criteria (older age, diabetes, TIMI risk score >3, Killip class >1, and anterior MI) and represents a subgroup of high-risk patients, which seems to be associated with poor myocardial reperfusion and worse outcome. The exact underlying mechanism explaining this type of distortion of the terminal portion of the QRS complex remains to be evaluated.

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CHAPTER 8

THE EXTENT OF ST ELEVATION AND ST DEVIATION AS PREDICTORS OF MORTALITY IN ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION PATIENTS PLANNED TO UNDERGO PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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ABSTRACT

PURPOSE

Few data exist on the predictive value of the extent of ST deviation in ST-elevation myocardial infarction (STEMI) patients. Therefore we have examined the predictive value of ST elevation and ST deviation in STEMI patients on 30-day and long term mortality.

METHODS

All STEMI patients with an interpretable diagnostic electrocardiogram (ECG), who were referred to the Isala hospital and were planned to undergo a primary percutaneous coronary intervention (pPCI) in the period 2001 until 2009, were prospectively registered in a cohort study. These patients were divided in tertiles based on the cumulative (cum) ST deviation and cum ST elevation, as assessed by an independent core-lab.

RESULTS

In total, 4513 patients were registered. 30-day mortality increased with cum ST deviation (0-9 mm: 1.9%, >9-16 mm: 2.4%, >16mm: 3.9%, p=0.001), but not significant with cum ST elevation. Long term mortality (median follow up time of 7.1 years) increased with cum ST-deviation (0-9 mm: 18.6%, >9-16 mm: 22.1%, >16 mm: 25.7%, p<0.001) and with cum ST-elevation (0-6 mm: 19.7%, >6-11 mm: 22.7%, >11 mm: 24.2%, p=0.070). After multivariable adjustment using Cox proportional Hazard models, cum ST deviation (T1: reference, T2: HR: 1.09 95% CI (0.67-1.77), T3: HR: 1.76 95% CI (1.14-2.73)) was independently associated with 30-day mortality. Both cum ST deviation (T1: reference, T2: HR:1.14 95% CI (0.98-1.34), T3: HR: 1.32 95% CI (1.13-1.53)) and ST elevation (T1: reference, T2: HR: 1.17 95% CI (1.00-1.38), T3: HR: 1.21 95% CI (1.04-1.42)) were independently associated with long term mortality.

CONCLUSION

Besides ST elevation, taking the extent of ST depression into account improves the predictive value of the diagnostic 12 lead ECG especially for 30-day mortality in STEMI patients who are planned to undergo pPCI.

INTRODUCTION

An electrocardiogram (ECG) represents a cheap and easy instrument to evaluate the risk of patients in the pre-hospital phase. Numerous specific markers on the ECG have been shown to predict clinical outcome for ST-segment elevation myocardial infarction (STEMI) patients, such as new left bundle branch block [1-2], the grade of ischemia [3-4], QRS width [1, 5], anterior myocardial infarction [1, 6] and ST elevation [1, 7-8]. Only few data are available on the predictive value of ST deviation (both ST elevation and depression) [1, 9-10]. Therefore, most treatment decisions in STEMI patients are not based upon the extent of this specific parameter. In fact, this marker might be very interesting, since acute transmural ischemia caused by occlusion of a major coronary artery produces an epicardial injury that can be detected as deviation of the ST-segment toward the involved myocardial region [11]. I.e. acute occlusion of the left anterior descending (LAD) or the right coronary artery (RCA) typically causes ST elevation while acute occlusion of the circumflex artery (CX) typically shows only ST depression in the 12 standard ECG leads [12]. Consequently, we hypothesized that it would be sufficient for the risk estimation of STEMI patients to also take ST depression into account besides ST elevation. The present study is conducted to investigate the predictive value of the extent of ST deviation as compared to the ST elevation in a large cohort of unselected STEMI patients.

METHODS

Patient population

All STEMI patients with an available and interpretable diagnostic ECG, who were transported to the Isala hospital and were planned to undergo a primary percutaneous coronary intervention (pPCI) in the period 2001 until 2009, were included in a cohort study. Criteria for the diagnosis of STEMI were: (1) history of cardiac symptoms of at least 30 min in the last 12 hours or between 12 and 24 hours if they had persistent symptoms with evidence of ongoing ischemia prior to presentation at the PCI centre or referral non-PCI centre, (2) elevated levels of Creatin Kinase or Creatin Kinase-MB and (3) concurrent ECG changes: ST elevation of >0.1mV in at least two adjacent ECG leads [13]. The municipal registration in the Netherlands was consulted for the mortality of all patients in this study. In case mortality could not be retrieved, patients were excluded from analysis. Patients with an uninterpretable diagnostic ECG, with an out of hospital cardiac arrest (OHCA) and patients of which the type of triage and transfer in the pre-hospital phase was unknown, were excluded. Infarct size was calculated as the peak level of CK (peak CK) within 24 hours after admission [14].

The included STEMI patients were divided in tertiles based on the cumulative (cum) ST deviation and based on cum ST elevation separately (T1, T2 and T3).

pPCI procedure

The staff of the catheterization laboratory of the PCI centre was pre-informed about the estimated time of arrival of the patient and was activated well before the arrival of the

patient. In case the staff lived more than 30 minutes away from the PCI centre, they had to stay in the PCI centre while being on-call. All patients were treated pre-hospital with an intravenous bolus of 5000 IU of unfractionated heparin and 500 mg aspirin intravenously. During the study period the administration of clopidogrel on top of aspirin and heparin as pre-hospital treatment was implemented from July first 2006. The administration of GPIIBIIIA blockers in the pre-hospital phase was left at the discretion of the referring physicians. The location of the acute vessel occlusion was determined in this study by the PCI operator.

Electrocardiographic analysis

All available and interpretable diagnostic ECGs were analyzed by an analyst of the independent ECG core-lab (Diagram BV) who had no knowledge of the patient's angiographic or clinical outcome. In case of doubt, a second core-lab analyst re-evaluated the ECG and consensus was reached in all cases. ST elevation was measured at the J-point in each lead, except aVR. ST deviation (ST elevation plus ST depression in all leads, except aVR) was measured 20 ms after the end of the QRS complex compared to the isoelectric line with a calliper.

Outcome measures

The endpoints of this study are 30-day and long-term mortality.

Time intervals

Four different time intervals were evaluated: 1. Time from symptom onset (SO) to diagnosis (SO-Diagnosis). 2. Time from diagnosis (time diagnostic ECG) to arrival PCI centre (Diagnosis-Door PCI) 3. Time from arrival PCI centre to Balloon inflation (BI) (Door-to-balloon: D2B) 4. Total ischemic time defined as the time from SO to BI.

Statistical analysis

Statistical analysis was performed with SPSS 20.0 (Chicago, Illinois). Continuous data were expressed as mean ± SD or median and interquartile range. Categorical data were presented as percentage. A Kruskal-Wallis test was used for continuous data, since they were non-Gaussian distributed. A Pearson's Chi-square test was used for categorical data. The continuous variable infarct size was converted into a dichotomous variable by dividing the continuous variable in interquartile ranges and defining the interquartile range 0.75-1.00 as large enzymatic infarct size (75^{th} percentile).

Cox proportional Hazard models were constructed to estimate the effect of cum ST deviation and cum ST elevation separately on 30-day and on long-term mortality. At first we corrected for confounders of the pre-hospital phase and secondly we corrected additionally for CX as infarct related vessel (IRV) and three vessel disease (VD).

Confounders included in the cum ST deviation model for 30-day mortality were age, killip class >1 and the tertiles of ST deviation. The same confounders were included for the model

for long term mortality, although previous myocardial infarction (MI) was included instead of age. Confounders included in the cum ST elevation model for 30-day mortality were smoking, hypercholesterolemia, previous MI, previous coronary artery bypass grafting (CABG) and killip class>1. For long term mortality the same confounders were included, nevertheless hypercholesterolemia was excluded. Confounders were only added to the Cox proportional Hazard models if they were considered as strong confounders.

In all the statistical analyses *p*-values <0.05 were considered as statistical significant. The study was conducted according to the principles of the Declaration of Helsinki and the protocol was approved by the local institutional review board. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

RESULTS

From 2001 until 2009, 6350 patients were referred to our hospital with the intention to perform pPCI. Of these, 773 patients (12.2%) had no (interpretable) diagnostic ECG, in 74 patients (1.2%) mortality could not be retrieved, 405 patients (6.4%) had an OHCA, in 382 (6.0%) the type of triage and transfer in the pre-hospital phase was unknown and 203 patients (3.2%) were self referring patients. The remaining 4513 patients were divided in tertiles based on cum ST deviation (T1: 0-9 mm, T2: >9-16 mm and T3: >16 mm) and divided in tertiles based on cum ST elevation (T1: 0-6 mm, T2: >6-11 mm and T3: >11 mm) at the diagnostic ECG. The median follow-up time was 7.1 (interquartile range 4.7-9.4) years.

Patient Characteristics

The baseline characteristics are described in Table 1. Age and smoking differed among the tertiles of cum ST deviation. Cum ST deviation was associated with a lower prevalence of hypercholesterolemia, previous CABG, PCI and MI, with no VD and less often with the CX as infarct related vessel. Killip class >1 increased with cum ST deviation.

The time intervals are described in Table 2. Time from diagnosis to arrival at the PCI center, D2B time and ischemic time decreased with cum ST deviation.

The baseline characteristics and time intervals for cum ST elevation are described in Table 1 and 2.

Infarct size and clinical outcome

Patients with high ST deviation (3rd tertile) more often had an occluded infarct related vessel (IRV), and a 2-fold larger infarct size. Both 30-day and long term mortality increased with cum ST deviation (Table 3 and Figure 1A).

Table 1. Baseline characteristics ST deviation and ST elevation

Characteristic	T1: ST dev 0-9 mm (n = 1622)	T2: ST dev >9-16 mm (n = 1455)	T3: ST dev >16 mm (n = 1436)	P	T1: ST ele 0-6 mm (n =1805)	T2: ST ele >6-11 mm (n =1289)	T3: ST ele >11 mm (n = 1419)	P
Male gender	1185/1622 (73.1%)	1057/1455 (72.6%)	1083/1436 (75.4%)	0.186	1314/1805 (72.8%)	948/1289 (73.5%)	1063/1419 (74.9%)	0.397
Age (mean ± SD)	62.2 ± 12.2	63.8 ± 12.5	63.1 ± 12.8	0.002	62.9 ± 12.2	63.4 ± 12.5	62.8 ± 12.9	0.328
Diabetes Mellitus	195/1613 (12.1%)	191/1450 (13.2%)	162/1432 (11.3%)	0.309	216/1794 (12.0%)	171/1285 (13.3%)	161/1416 (11.4%)	0.297
Smoking	711/1587 (44.8%)	607/1419 (42.8%)	678/1400 (48.4%)	0.009	788/1761 (44.7%)	563/1258 (44.8%)	645/1387 (46.5%)	0.555
Hypertension	572/1600 (35.8%)	492/1444 (34.1%)	499/1419 (35.2%)	0.619	636/1782 (35.7%)	438/1278 (34.3%)	489/1403 (34.9%)	0.711
Hypercholesterolemia	417/1545 (27.0%)	305/1373 (22.2%)	266/1346 (19.8%)	<0.001	452/1717 (26.3%)	274/1218 (22.5%)	262/1329 (19.7%)	<0.001
Previous CABG	76/1620 (4.7%)	52/1452 (3.6%)	37/1433 (2.6%)	0.008	105/1801 (5.8%)	35/1286 (2.7%)	25/1418 (1.8%)	<0.001
Previous PCI	173/1617 (10.7%)	113/1449 (7.8%)	92/1431 (6.4%)	<0.001	199/1799 (11.1%)	94/1283 (7.3%)	85/1415 (6.0%)	<0.001
Previous MI	207/1619 (12.8%)	163/1448 (11.3%)	119/1431 (8.3%)	<0.001	244/1800 (13.6%)	125/1282 (9.8%)	120/1416 (8.5%)	<0.001
Killip >1	75/1617 (4.6%)	77/1450 (5.3%)	111/1423 (7.8%)	0.001	97/1797 (5.4%)	63/1286 (4.9%)	103/1407 (7.3%)	0.016
No VD	59/1589 (3.7%)	33/1442 (2.3%)	20/1418 (1.4%)	<0.001	47/1771 (2.7%)	33/1274 (2.6%)	32/1404 (2.3%)	0.784
3VD	305/1589 (19.2%)	303/1442 (21.0%)	303/1418 (21.4%)	0.279	409/1771 (23.1%)	256/1274 (20.1%)	246/1404 (17.5%)	0.001
CX related vessel	264/1566 (16.9%)	198/1430 (13.8%)	164/1416 (11.6%)	<0.001	346/1750 (19.8%)	172/1266 (13.6%)	108/1396 (7.7%)	<0.001

CABG: coronary artery bypass grafting, CX: circumflex, Dev: deviation, Ele: elevation, MI: myocardial infarction, PCI: percutaneous coronary intervention, SD: standard deviation, VD: vessel disease.

Table 2. Time intervals ST deviation and ST elevation

	T1: ST dev 0-9 mm (n = 1622)	T2: ST dev >9-16 mm (n = 1455)	T3: ST dev >16 mm (n = 1436)	P
Time interval				
Ischemic time (median, IQR)	235.0 (166.0-380.8) n=1510	210.0 (155.0-325.5) n=1393	203.0 (149.0-291.0) n=1355	<0.001
SO-Diagnosis (median, IQR)	108.0 (56.0-237.5) n=1081	97.0 (53.8-193.3) n=970	100.5 (53.0-185.8) n=864	0.037
Diagnosis-Door PCI (median, IQR)	63.0 (44.0-98.0) n=1078	57.0 (39.0-81.3) n=970	56.0 (42.0-79.0) n=859	<0.001
D2B (median, IQR)	50.0 (31.0-80.3) n=1390	44.0 (30.0-65.0) n=1299	42.0 (29.0-61.0) n=1288	<0.001
	T1: ST ele 0-6 mm (n =1805)	**T2: ST ele >6-11 mm (n =1289)**	**T3: ST ele >11 mm (n = 1419)**	**P**
Ischemic time (median, IQR)	230.0 (165.0-368.0) n=1687	216.0 (154.0-320.0) n=1231	200.0 (149.0-292.8) n=1340	<0.001
SO-Diagnosis (median, IQR)	106.0 (55.0-222.0) n=1222	100.0 (54.0-199.5) n=853	95.0 (53.0-180.8) n=840	0.080
Diagnosis-Door PCI (median, IQR)	63.0 (43.0-97.0) n=1215	55.0 (39.0-80.0) n=855	57.0 (42.0-79.0) n=837	<0.001
D2B (median, IQR)	50.0 (32.8-79.0) n=1554	43.0 (28.0-64.0) n=1153	42.0 (29.0-60.0) n=1270	<0.001

Dev: deviation, D2B: door-to balloon, Ele: elevation, IQR: interquartile range, PCI: percutaneous coronary intervention, SO: symptom onset.

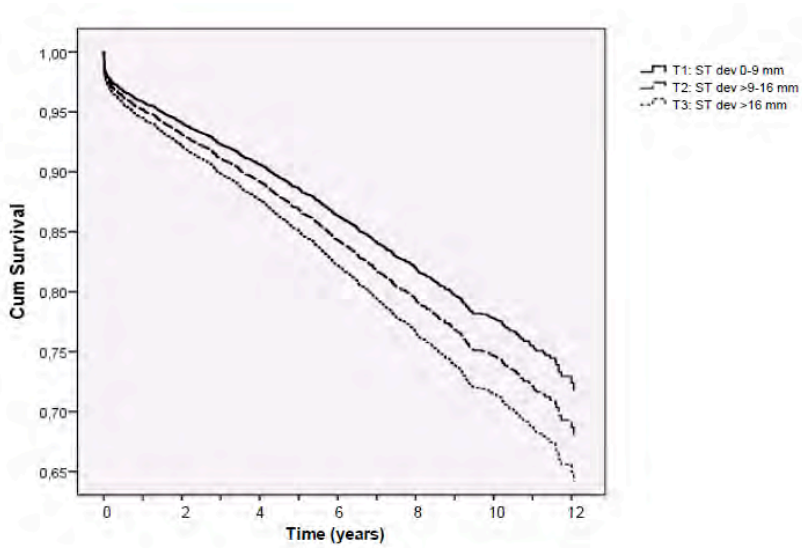
Table 3. Angiographic and clinical outcome ST deviation and ST elevation

Characteristic	T1: ST dev 0-9 mm (n = 1622)	T2: ST dev >9-16 mm (n = 1455)	T3: ST dev >16 mm (n = 1436)	P	T1: ST ele 0-6 mm (n =1805)	T2: ST ele >6-11 mm (n =1289)	T3: ST ele >11 mm (n = 1419)	P
TIMI flow 2/3 pre-PCI	544/1417 (38.4%)	483/1325 (36.5%)	410/1337 (30.7%)	<0.001	611/1586 (38.5%)	419/1173 (35.7%)	407/1320 (30.8%)	<0.001
TIMI flow 2/3 post-PCI	1371/1409 (97.3%)	1272/1312 (97.0%)	1284/1328 (96.7%)	0.639	1529/1570 (97.4%)	1122/1166 (96.2%)	1276/1313 (97.2%)	0.188
Infarct size (mean ± SD, IU/L, n)*	931.0 ± 1585.1 (n=1572)	1480.0 ± 1775.8 (n=1429)	2220.0 ± 2556.9 (n=1401)	<0.001	1493.7 ± 1555.8 (n=1758)	1951.3 ± 1822.9 (n=1265)	2840.0 ± 2587.5 (n=1379)	<0.001
Infarct size >75th percentile	194/1572 (12.3%)	350/1429 (24.5%)	557/1401 (39.8%)	<0.001	243/1758 (13.8%)	301/1265 (23.8%)	557/1379 (40.4%)	<0.001
30 day mortality	31/1622 (1.9%)	35/1455 (2.4%)	56/1436 (3.9%)	0.001	45/1805 (2.5%)	28/1289 (2.2%)	49/1419 (3.5%)	0.094
Long term mortality	301/1622 (18.6%)	322/1455 (22.1%)	369/1436 (25.7%)	<0.001	356/1805 (19.7%)	292/1289 (22.7%)	344/1419 (24.2%)	0.070

*peak CK

Dev: deviation, Ele: elevation, PCI: percutaneous coronary intervention, SD: standard deviation, TIMI: thrombolysis in myocardial infarction.

After multivariable adjustment using Cox proportional Hazard models for several pre-hospital confounders cum ST deviation was independently associated with 30-day mortality (T1: reference, T2: HR: 1.09 95% CI (0.67 to 1.77), T3: HR: 1.76 95% CI (1.14 to 2.73)) and with long term mortality (T1: reference, T2: HR: 1.14 95% CI (0.98 to 1.34), T3: HR: 1.32 95% CI (1.13 to 1.53)). After additional correction for the CX as IRV and three VD the effect was more pronounced (see Table 4). The effects of cum ST elevation on infarct size and clinical outcome are depicted in Figure 1 B, Table 3 and 4.



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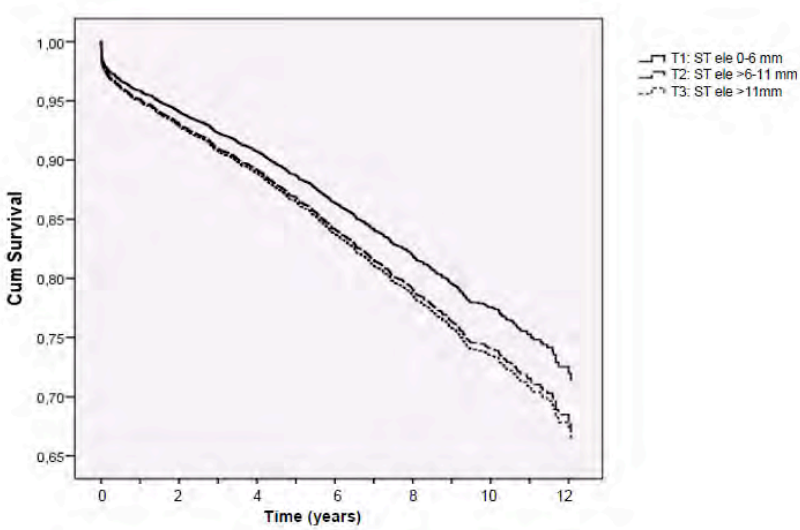

B

Figure 1.

Cox regression curve of cum ST deviation (A) and cum ST elevation (B).

Table 4. Cox regression analyses for ST deviation and ST elevation

	ST deviation	
	30-day mortality HR (95% CI)	**Long term mortality HR (95% CI)**
Unadjusted effect	T1: reference	T1: reference
	T2: HR 1.26 95% CI (0.78 to 2.05)	T2: HR 1.16 95% CI (1.00 to 1.36)
	T3: HR 2.06 95% CI (1.33 to 3.20)	T3: HR 1.33 95% CI (1.15 to 1.55)
Correction for confounders	T1: reference	T1: reference
pre-hospital phase	T2: HR 1.09 95% CI (0.67 to 1.77)	T2: HR 1.14 95% CI (0.98 to 1.34)
	T3: HR 1.76 95% CI (1.14 to 2.73)	T3: HR 1.32 95% CI (1.13 to 1.53)
Correction for confounders	T1: reference	T1: reference
pre and in-hospital phase	T2: HR 1.16 95% CI (0.67 to 2.01)	T2: HR 1.14 95% CI (0.97 to 1.35)
(CX as IRV and 3VD)	T3: HR 2.03 95% CI (1.24 to 3.33)	T3: HR 1.32 95% CI (1.13 to 1.55)
	ST elevation	
	30-day mortality HR (95% CI)	**Long term mortality HR (95% CI)**
Unadjusted effect	T1: reference	T1: reference
	T2: HR 0.87 95% CI (0.54 to 1.40)	T2: HR 1.10 95% CI (0.94 to 1.28)
	T3: HR 1.39 95% CI (0.93 to 2.08)	T3: HR 1.15 95% CI (0.99 to 1.33)
Correction for confounders	T1: reference	T1: reference
pre-hospital phase	T2: HR 0.95 95% CI (0.58 to 1.54)	T2: HR 1.17 95% CI (1.00 to 1.38)
	T3: HR 1.27 95% CI (0.82 to 1.96)	T3: HR 1.21 95% CI (1.04 to 1.42)
Correction for confounders	T1: reference	T1: reference
pre and in-hospital phase	T2: HR 1.14 95% CI (0.68 to 1.94)	T2: HR 1.18 95% CI (1.00 to 1.39)
(CX as IRV and 3VD)*	T3: HR 1.44 95% CI (0.88 to 2.35)	T3: HR 1.21 95% CI (1.03 to 1.42)

*For long term mortality only additionally corrected for CX as IRV.

CI: confidence interval, CX: circumflex, IRV: infarct related vessel, HR: hazard ratio, VD: vessel disease.

DISCUSSION

To our knowledge this is the first study to investigate the extent of cum ST deviation and cum ST elevation on the diagnostic ECG on 30-day and long term mortality in a large cohort of STEMI patients. The main finding is that both parameters are strongly associated with infarct size and independently predict long term mortality. However, taking the extent of ST segment depression into account, by looking at ST deviation and not merely ST elevation, seems to improve the predictive value. Furthermore, we have shown that after correction for CX as infarct related vessel, these effects were even more pronounced.

Our results are in concordance with previous trials, although only several trials have investigated this issue. Hathaway et al. have shown in their large retrospective analysis of the GUSTO-1 trial, that ST deviation assessed on the initial ECG was a predictor of 30-day mortality, although no comparison was made between the predictive effect of ST deviation and ST elevation [1]. Furthermore, Martin et al. demonstrated in a cohort of STEMI and non-STEMI patients that the consideration of both ST elevation and ST depression in the standard 12 lead ECG recording significantly increases the sensitivity for the detection of STEMI with only a slight decrease in the specificity [9]. Although the predictive effect of ST deviation on mortality was not assessed, they validated the application of ST depression criteria with contrast-enhanced cardiac magnetic resonance imaging as the diagnostic gold standard. Knot

et al. established in a cohort of STEMI and non-STEMI patients that similar strategies (emergency angiography with PCI whenever feasible) should be applied to both types of acute MI, since a MI with ST depression may represent a similar risk as a ST elevation acute MI [10].

Characteristics of patients

We found some contradiction in the risk of patients in the different tertiles of ST deviation/elevation. Patients in the lower tertiles had more baseline risk factors: they more often had hypercholesterolemia, a previous MI and underwent previous revascularization (PCI and CABG), whereas patients in the higher tertiles had more angiographic and clinical risk factors: they more often had an occluded IRV pre-PCI and more often presented with signs of heart failure. After multivariable adjustment, ST deviation independently predicted 30-day mortality, and both ST deviation and ST elevation independently predicted long term mortality.

Time to treatment

Overall, the time intervals decreased with cum ST deviation and cum ST elevation. This is of utmost importance, especially for patients of the highest tertiles, because with a higher extent of ST deviation or ST elevation outcome worsens. Highly trained paramedics and physicians in our area focus already on timely treatment for the high risk patients, although it could be decreased even more. In our study the difference in DTB time between the first and the third tertile was only 8 minutes. For patients with more than 15 mm ST deviation on the diagnostic ECG, every effort should be made to decrease time to reperfusion as short as possible. A time from Diagnosis-Door PCI of <40 minutes and a D2B time <30 minutes should be the standard goal for these patients.

CX as IRV and three VD

We expected on forehand an interaction effect between the CX as IRV and the tertiles of cum ST deviation on 30-day mortality and on long term mortality, since an acute occlusion of the CX typically produces only ST depression in the 12 standard ECG leads, however this effect could not be demonstrated. Nevertheless, after multivariable adjustment for CX as IRV and three VD, the effect of cum ST deviation and cum ST elevation on mortality (30-day and long term) was more pronounced. These results are in concordance with the results of Rasoul et al. They have demonstrated that patients with the CX as IRV, have a significantly worse clinical outcome [15].

Besides CX as IRV, three VD was also a strong predictor for 30-day and long term mortality. In general, patients affected with three VD have a larger infarction area at risk and therefore usually present with more ST depression and ST elevation, compared to patients with one or two vessel disease.

Clinical outcome ST deviation versus ST elevation

ST deviation is a predictor for 30-day and long term mortality, whereas ST elevation only predicts long term mortality. Despite the fact that the pathogenesis of concomitant ST depression in STEMI patients is still a matter of debate (reciprocal image of ST elevation in the infarct zone, additional ischemia beyond the infarct zone or more extensive infarction), several studies have demonstrated its prognostic impact in patient with ST elevation [16-18]. Therefore, it is plausible that beyond ST elevation also taking ST depression (ST deviation) in to account for the evaluation of myocardial perfusion gives more additional prognostic information in comparison with only ST elevation.

Limitations

At first, a major limitation of the current study is that up to 12.2% of the total population needed to be excluded because of missing or inadequate diagnostic ECGs. Secondly, since the project was not randomized and was dispersed over several years, consequently the risk of unknown confounders exists. Thirdly, the level of peak CK within 24 hrs was used as surrogate parameter for infarct size. Fourthly, to answer our research question it would probably be more suitable to develop prediction models, instead of association models. However the constructed prediction models could not be validated successfully in an external database, because we had no access to an external database which included ≥ 100 cases and non-cases [19].

Conclusion

Besides ST elevation, taking the extent of ST depression into account improves the predictive value of the diagnostic 12 lead ECG especially for 30-day mortality in STEMI patients who are planned to undergo pPCI.

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SUMMARY AND FUTURE PERSPECTIVES

SUMMARY

In **PART I** of the thesis, we have focussed on the pre-hospital diagnosis and triage in the ambulance (field triage) and pre-hospital treatment of ST-segment elevation myocardial infarction (STEMI) patients. The following items were investigated: type of transfer, residential distance, time delays and treatment strategies.

In the introduction of the thesis (**chapter 1**), the current status of field triage and pre-hospital treatment in STEMI patients was reviewed. An overview was constituted concerning pre-hospital infarct diagnosis and type of transfer, the organisation of networks, pre-hospital risk assessment and triage, time delays to treatment and pre-hospital treatment strategies including the thrombolytic therapy and antithrombotic agents.

In **chapter 2**, referral of STEMI patients via field triage with direct transfer to a percutaneous coronary intervention (PCI) centre was compared to referral via non-PCI centres. It was demonstrated in a STEMI population of 5128 patients, that field triage resulted in a shorter ischemic time (OR for ischemic time <3 hours: 2.45, 95% CI 2.13-2.83), a smaller infarct size (OR for peak creatin kinase (CK) below the median for the total group: 1.19, 95% CI 1.04-1.36) and a lower one year mortality (OR: 0.67, 95% CI 0.50-0.91). The benefits of field triage were more pronounced with longer distance from the patient's residence to the nearest PCI centre. In addition, this type of triage increased the number of patients eligible to treatment according to the American and European guidelines. These results suggest that living at a longer distance from a PCI center may not negatively influence clinical outcomes when field triage with direct transfer to a PCI centre is available.

In **chapter 3** a similar comparison was made as in chapter 2 by systematic review. After literature search 14 randomized clinical trials (RCTs) were included in the systematic review, consisting of 20 treatment groups and 4474 participants. After multivariable frequency weighted logistic regression analysis it was revealed that field triage with direct transfer to a PCI centre was associated with a marked lower incidence of 30 day mortality (OR:0.58, 95% CI 0.37-0.89). Therefore, field triage with direct ambulance transport to a PCI hospital should become the treatment of choice for STEMI patients.

The results of the comparison made in chapter 2 interested and encouraged us to investigate the relation between residential distance and ischemic time in more detail. We therefore examined this relation in a large cohort of 4149 STEMI patients in **chapter 4**. It was revealed that a longer distance from a patient's residence to a PCI centre was associated with an increase in ischemic time in patients referred via a non-PCI centre (OR=1.11 95% CI 1.01-1.12 for >60-90km compared to 0-30km). This effect was not demonstrated at a shorter distance or in patients referred via field triage. It was concluded that referral via field triage

did not lead to a significant increase in ischemic time, especially at long distances of up to 90km.

System delay is defined as the time from first contact with the health care system to initiation of reperfusion therapy. It is currently one of the most interesting and highlighted time delays to treatment, because it can be minimised by optimizing the system. Several years ago it was demonstrated that system delay was associated with a higher incidence of mortality [1]. Since we expected that this effect would be more apparent in patients at high risk for large infarctions, we have investigated the influence of system delay on mortality in anterior versus non-anterior STEMI patients representing high and lower risk patients respectively, in **chapter 5**. In total, 3041 patients were included in our study consisting of 1253 patients with an anterior MI and 1788 with a non-anterior MI. These patients were divided into quartiles of system delay: Q1 for lowest to Q4 for highest quartile. It was demonstrated that prolonged system delay was associated with a higher 30 day mortality (Q1: reference, Q2: HR 1.18, 95% CI 0.46-3.00; Q3: HR 2.45, 95% CI 1.07-5.63; Q4: HR 2.25, 95% CI 0.97-5.25) and long term mortality (Q1: reference, Q2: HR 1.09, 95% CI 0.71-1.68; Q3: HR 1.68, 95% CI 1.13-2.49; Q4: HR 1.55, 95% CI 1.03-2.33) in patients with an anterior MI. This effect was not shown in patients with a non-anterior MI. Therefore, we believe it is of the greatest importance to minimize system delay in STEMI patients who present with an anterior MI.

Besides the type of referral, residential distance to a PCI centre and time intervals, pre-hospital treatment strategies are also very important for the outcome of STEMI patients. Pretreatment with a thienopyridine, like clopidogrel, on top of aspirin and heparin (prior to PCI) was common practice in many countries for numerous years [2]. Currently, the new P2Y12 receptor inhibitors ticagrelor and prasugrel, are preferred over clopidogrel [3]. However, at the time this study was performed, clopidogrel was the treatment of choice. Since definitive evidence for pre-hospital treatment strategies was lacking, this topic was investigated in **chapter 6**. In a STEMI population of 2475 patients we demonstrated that pre-hospital treatment with a high dose (HD) of clopidogrel (600 mg) did not improve pre-PCI thrombolysis in myocardial infarction (TIMI) flow compared to in-hospital treatment (OR: 1.18, 95% CI 0.96-1.44) after multivariable adjustment for relevant confounders. Nevertheless, pretreatment with clopidogrel was associated with a lower incidence of recurrent myocardial infarctions (MIs) at 30 days (HR: 0.45, 95% CI 0.22-0.93) and at one year (HR: 0.45, 95% CI 0.25-0.80). No difference in post PCI TIMI 2/3 flow, major bleeding, mortality, major adverse cardiac events (MACE) and the combination of mortality and recurrent MI at 30 days and at one year was present between the two groups. Therefore, early administration of HD clopidogrel appears to have net clinical benefit.

In **PART II** of the thesis predictors for STEMI patients at risk were investigated. We examined two determinants depicted on the diagnostic ECG that were associated with high risk of 30 day mortality and/or failure of ST-segment resolution (STR) one hour post PCI in STEMI patients.

The study described in **chapter 7** was a sub study of the On-TIME 2 trial and was performed to explore which baseline characteristic of STEMI patients are associated with grade 3 ischemia (G3I: distortion of the terminal portion of the QRS complex). It was demonstrated that patients with G3I were older, more often male, more often had diabetes, a TIMI risk score >3, an anterior infarction, three vessel disease, more often presented in Killip class >1, pre-procedural TIMI flow <3 and myocardial blush grade <3 post PCI. Furthermore, it was demonstrated that at one hour post PCI, residual ST deviation was higher in patients with G3I compared to patients with grade 2 ischemia and G3I was associated with a higher incidence of MACE. After multivariable adjustment, G3I was an independent predictor of failure of STR at one hour post PCI (OR: 1.4, 95% CI 1.1-1.9) and 30 day mortality (OR: 3.2; 95% CI 1.2-8.7).

Since many years ST elevation is an important parameter for treatment decisions in STEMI patients. A disadvantage of this parameter is that not all acute occlusions lead to ST elevation. I.e. in patients with an acute occlusion of the circum flex artery ST depressions are frequently present. Only few data exist about the extent of ST elevation and ST deviation as predictors of mortality in STEMI patients. Therefore, we investigated this topic in a large population of STEMI patients (n=4513) (**chapter 8**). It was demonstrated that the extent of cum ST deviation predicts 30-day mortality (T1: reference, T2: OR: 1.09 95% CI (0.67-1.77), T3: OR 1.76 95% CI (1.14-2.73)). The extent of both cum ST elevation (T1: reference, T2: OR: 1.17 95% CI (1.00-1.38), T3: OR: 1.21 95% CI (1.04-1.42)) and cum ST deviation (T1: reference, T2: OR: 1.14 95% CI (0.98-1.34), T3: OR: 1.32 95% CI (1.13-1.53)) predicts long term mortality (median: 7.1 years, IQR: 4.7-9.4). Therefore, besides ST elevation also taking the extent of ST depression into account improves the predictive value of the diagnostic 12 lead ECG especially for 30-day mortality in STEMI patients who are planned to undergo pPCI.

FUTURE PERSPECTIVES

Over the past two decennia much effort has been made concerning the treatment of STEMI patients, although there is still room and necessity for improvement. An increasing interest has been shown in the pre-hospital diagnosis, triage, and treatment of STEMI patients.

Field triage

Several trials, including our cohort study and systematic review, have demonstrated that field triage with direct transfer to a PCI centre improves clinical outcomes for STEMI patients [4-5]. Therefore, more effort should be put into direct transfer worldwide. Consequently, it is important to make patients and general practitioners aware of the benefits of this type of transfer compared to self-referring and referring via general practitioners or via a non-PCI center. Furthermore, it is essential for the diagnosis of STEMI patients that electrocardiogram (ECG) equipment with a computerized electrographic algorithm or telecommunication (referred to as 'telemedicine') is available to reach an accurate diagnosis. In fact, failure of the pre-hospital diagnosis is one of the main reasons why STEMI patients are initially transferred to a non-PCI centre [6]. Therefore, adequate training of (para)medics is of utmost importance. In addition, it would be interesting to explore further reasons why patients are not transferred to a PCI centre directly and if possible develop solutions to these issues.

Determinants timely access PCI centre

The distance that a patient has to cover to reach a PCI centre is a potential determinant of outcome that has not been studied in the same detail as the effect of different time intervals [1, 7-13]. As demonstrated in two of our studies, at long residential distances referral via field triage did not lead to an increase in time to treatment compared to short distance. In fact, the benefits of field triage were more pronounced at long residential distances [4, 12]. Therefore, it might be interesting to incorporate residential or 'true' travel distance together with type of transfer, beyond time intervals, in the decision making of timely reperfusion therapy for STEMI patients. Controversially, expansion of PCI centres may play less a role in the overall improvement of timely treatment of STEMI patients, since Concannon et al. and Horwitz et al. both demonstrated that opening new PCI centres did not help patients to gain timely access to PCI [14-15]. In addition, our results demonstrated that residential distance is not significantly associated with total ischemic time if patients are transferred via field triage [12]. The number, availability and expertise of the interventional cardiologists also plays an important role in providing timely access to PCI as well as the expertise of ambulance personnel. In the future more attention is needed on changes in PCI capacity and on the effects of these changes on outcome measures as well as on the selection of high-risk patients for transfer.

Time delays to treatment

Aiming for short time intervals will remain a topic of great importance, especially in high risk patients [16]. Since the time from symptom onset to call for help and diagnosis is usually very long, it is likely that there is much health gain to be expected in shortening this time delay. Therefore, more attention should be given to awareness of the symptoms of MI by the national and regional health care programs. Furthermore, as described earlier, direct transfer to a PCI center after field triage is an important predictor of timely treatment and improves clinical outcome, and should therefore preferably be implemented worldwide if the landscape, traffic and weather conditions allow this type of transfer.

Pre-hospital treatment

There is a clear lack of evidence into the efficacy of pre-hospital treatment, while there is much to gain by improving this treatment. For example for the COX-1 inhibitor, aspirin, the pre-hospital treatment effect has not been studied individually and for clopidogrel several cohort studies, one systematic review and only one underpowered RCT have been performed [17-26]. It is highly unlikely that new RCTs investigating pre-hospital treatment of clopidogrel will be designed. However, for the novel antithrombotic agents this might be the case. Currently two studies have investigated the pre-hospital administration of bivalirudin and ticagrelor. The first results of the Euromax trial demonstrated that pre-hospital administration of the direct thrombin inhibitor, bivalirudin, reduced major bleeding compared with both patients treated with heparin only plus bailout glycoprotein IIb/IIIa inhibitors (GPI), but increased acute stent thrombosis. The latter was probably the result of the combination of delayed bioavailability and rapid clearance [27]. The Atlantic trial investigated pre- versus in-hospital treatment with the reversible ADP receptor antagonist ticagrelor, which together with prasugrel is the preferred P2Y12 receptor inhibitor according to the current guidelines [2]. It was demonstrated that prehospital administration of ticagrelor in patients with acute STEMI appeared to be safe, but did not improve pre-PCI coronary reperfusion [28]. Despite the evidence for GPI from the On-TIME 2 trial [29], the most recent European guideline and the American guideline concluded that the administration of pre-hospital GPI is of uncertain benefit [30].

Given the importance of timely treatment of MI, preferably started in the pre-hospital phase, it would be desirable to explore the possibility of pre-hospital treatment with the newer antithrombotic agents. Furthermore, it has to be kept in mind that reduction of bleeding is of equal importance as reduction of ischemic events as well as that interindividual differences in the response to the agents are present in STEMI patients. Treatment strategies will likely become more tailored to the individual patient, considering the interindividual variability in response to antithrombotic agents and the patient's risk of bleeding.

ECG parameters

Finally, risk assessment in the acute phase is critical to facilitate optimal treatment and appropriate intensity of monitoring. The ECG is a cheap and easy instrument to evaluate this risk, and several specific markers on the ECG predict clinical outcome of STEMI patients. More effort should be put into use of the ECG and specifically into several markers on the ECG, like G3I and ST deviation beyond ST elevation [31-32]. These markers might be implemented in routine practice besides the current parameters, by implementation in algorithms of the ECG equipment for risk assessment of STEMI patients and in the training of (para)medics. Furthermore, more studies should be performed to evaluate whether telemedicine can further improve the pre-hospital diagnosis in STEMI patients.

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NEDERLANDSE SAMENVATTING

In **DEEL I** van dit proefschrift hebben we gefocust op de pre-hospitale diagnose en triage in de ambulance (veld triage) en op de pre-hospitale behandeling van ST-segment elevatie myocard infarct (STEMI) patiënten. De volgende onderwerpen werden onderzocht: type transport, woonafstand, tijdsintervallen en behandelstrategieën.

De introductie van dit proefschrift (**hoofdstuk 1**) is een review over de huidige status van veld triage en de pre-hospitale behandeling van STEMI patiënten. Er is een overzicht gegeven van de pre-hospitale infarct diagnose en het type transport, de organisatie van netwerken, de pre-hospitale risicostratificatie en triage, de tijdsintervallen tot behandeling en de pre-hospitale behandelstrategieën inclusief trombolytica en trombocytenaggregatieremmers.

In **hoofdstuk 2** werd verwijzing via veld triage met direct transport naar een percutaan coronair interventie (PCI) centrum vergeleken met verwijzing via een non-PCI centrum in STEMI patiënten. We hebben aangetoond in een STEMI populatie van 5128 patiënten, dat veld triage resulteert in een kortere ischemische tijd (odds ratio (OR) voor ischemische tijd <3 uur: 2.45, 95% BI 2.13-2.83), een kleinere infarctgrootte (OR voor piek creatine kinase (CK) minder dan de mediaan van de totale groep: 1.19, 95% BI 1.04-1.36) en een lagere mortaliteit op één jaar (OR: 0.67, 95% BI 0.50-0.91). De voordelen van veld triage werden duidelijker zichtbaar bij een langere woonafstand gemeten van patiënten hun huis tot het PCI centrum. Daarnaast hebben we aangetoond dat veld triage leidt tot een hoger aantal patiënten dat wordt behandeld volgens de Amerikaanse en Europese richtlijnen. De resultaten suggereren dat het wonen op een grote afstand van een PCI centrum niet per se een negatieve invloed heeft op klinische uitkomsten als veld triage met direct transport naar een PCI centrum voorhanden is.

In **hoofdstuk 3** is een overeenkomende vergelijking uitgevoerd als in hoofdstuk 2. Er is echter gebruik gemaakt van een ander studie design, namelijk van een systematische review. Na literatuuronderzoek hebben we 14 gerandomiseerde klinische trials (RCT's) geïncludeerd in de systematische review, bestaande uit 20 behandelgroepen en 4474 patiënten. Na het uitvoeren van een multivariabele frequentie gewogen logistische regressie analyse is gebleken dat veld triage met direct transport naar een PCI centrum was geassocieerd met een lagere 30-dagen mortaliteit (OR:0.58, 95% BI 0.37-0.89). Daarom zijn wij van mening dat veld triage met direct ambulance transport naar een PCI centrum het type transport zou moeten zijn waarmee STEMI patiënten naar een PCI centrum worden vervoerd.

De resultaten van de vergelijking die gemaakt is in hoofdstuk 2 hebben ons aangemoedigd om de relatie tussen woonafstand en ischemische tijd verder te onderzoeken (**hoofdstuk 4)**. We hebben aangetoond in een cohort van 4149 STEMI patiënten dat een langere woonafstand was geassocieerd met een toename in ischemische tijd in patiënten die werden verwezen via een non-PCI centrum (OR=1.11 95% BI 1.01-1.12 voor >60-90km in vergelijking met 0-

30km). Dit effect kon niet aangetoond worden bij een kortere afstand of in patiënten die werden verwezen via veld triage. Onze conclusie was dat verwijzing via veld triage niet tot een significante langere ischemische tijd leidt, met name op grote afstanden (tot 90 km).

Het zogenaamde 'system delay' is gedefinieerd als de tijd tussen het eerste medische contact en het moment van reperfusie. Het is momenteel één van de tijdsintervallen die de meeste belangstelling krijgt, omdat het kan worden geminimaliseerd door optimalisatie van het systeem. Een aantal jaren geleden is aangetoond dat 'system delay' was geassocieerd met een hogere mortaliteit [1]. Aangezien we verwachten dat dit effect duidelijker naar voren komt bij patiënten met een hoog risico voor grote MI's, hebben we de invloed van system delay op mortaliteit onderzocht in **hoofdstuk 5** in STEMI patiënten met een voorwandinfarct versus geen voorwand infarct respectievelijk hoog versus laag risico patiënten.
In totaal werden er 3041 patiënten geïncludeerd in onze studie, waarvan 1253 met een anterior MI en 1788 patiënten met een non-anterior MI. Deze patiënten hebben we vervolgens ingedeeld in kwartielen (K1: laagste kwartiel, K4: hoogste kwartiel). We hebben aangetoond dat een lange system delay geassocieerd was met een hogere 30-dagen mortaliteit (K1: referentie; K2: HR 1.18, 95% BI 0.46-3.00; K3: HR 2.45, 95% BI 1.07-5.63; K4: HR 2.25, 95% BI 0.97-5.25) en langere termijn mortaliteit (K1: referentie, K2: HR 1.09, 95% BI 0.71-1.68; K3: HR 1.68, 95% BI 1.13-2.49; K4: HR 1.55, 95% BI 1.03-2.33) in patiënten met anterior MI. Dit effect werd niet aangetoond bij patiënten met een non-anterior MI. Daarom zijn wij van mening dat het van groot belang is om system delay te minimaliseren in STEMI patiënten met een anterior MI.

Naast het type van verwijzing, de woonafstand naar een PCI centrum en tijdsintervallen, zijn de pre-hospitale behandelstrategieën ook erg belangrijk voor de uitkomsten van STEMI patiënten. De behandeling vóór aankomst in het PCI centrum (voorbehandeling) met een thiënopyridine, zoals clopidogrel, bovenop aspirine en heparine (toegediend vóór de PCI) was een gebruikelijke behandeling in vele landen voor meerdere jaren [2]. Momenteel hebben de nieuwe P2Y12 receptor inhibitors, ticagrelor en prasugrel, de voorkeur in plaats van clopidogrel [3]. Echter, op het moment dat dit onderzoek werd uitgevoerd, was clopidogrel de eerste keuze van P2Y12 receptor inhibitors volgens de richtlijnen. Aangezien sluitend bewijs voor de voorbehandeling ontbrak, hebben we dit onderwerp onderzocht in **hoofdstuk 6**. In een STEMI populatie van 2475 patiënten hebben we aangetoond dat voorbehandeling met een hoge dosis (HD) clopidogrel (600 mg) niet leidde tot een verbeterde thrombolysis in myocardial infarction (TIMI) flow pre-PCI in vergelijking met in-hospitale behandeling met clopidogrel (geen voorbehandeling) (OR: 1.18, 95% BI 0.96-1.44). Echter, voorbehandeling met clopidogrel was geassocieerd met een lagere incidentie van myocardinfarcten (MI's) op 30 dagen (HR: 0.45, 95% BI 0.22-0.93) en op één jaar (HR: 0.45, 95% BI 0.25-0.80). Er was geen verschil in TIMI 2/3 flow post PCI, grote bloedingen, mortaliteit, major adverse cardiac events (MACE) en de combinatie van mortaliteit en MI's op 30 dagen en op één jaar tussen de

twee groepen. Concluderend blijkt voorbehandeling met HD clopidogrel te leiden tot een netto klinisch voordeel.

In **DEEL II** van dit proefschrift werden voorspellers onderzocht van hoog risico patiënten. We hebben twee determinanten van het diagnose ECG onderzocht die geassocieerd waren met een hoog risico op 30-dagen mortaliteit en/of het ontbreken van ST-segment resolutie (STR) 1 uur na PCI.

Het onderzoek beschreven in **hoofdstuk 7** is een substudie van de On-TIME 2. We hebben onderzocht welke baselinekarakteristieken van STEMI patiënten geassocieerd zijn met graad 3 ischemie (G3I: vervorming van het laatste gedeelte van het QRS complex). We hebben aangetoond dat patiënten met G3I zich presenteerden met de volgende kenmerken: hoge leeftijd, mannelijk geslacht, diabetes, TIMI risico >3, anterior MI, drievatslijden, Killip klasse >1, pre-procedurele TIMI flow <3 en een myocardial blush grade <3 na PCI. Daarnaast hebben we aangetoond dat 1 uur na PCI residuele ST deviatie hoger was in patiënten met G3I in vergelijking met patiënten met graad 2 ischemie en dat G3I geassocieerd was met een hogere incidentie van MACE. Na multivariabele correctie was G3I een onafhankelijke voorspeller voor 30-dagen mortaliteit (OR: 3.2; 95% BI 1.2-8.7) en voor het ontbreken van STR 1 uur na PCI (OR: 1.4, 95% BI 1.1-1.9).

Sinds vele jaren is ST elevatie een belangrijke parameter voor beslissingen aangaande de behandeling van STEMI patiënten. Een nadeel van deze parameter is dat niet alle acute occlusies leiden tot ST elevatie. Een acute occlusie van de circum flex is namelijk vaak geassocieerd met ST depressies. Tot nu toe is er weinig onderzoek gedaan naar de grootte van cumulatieve ST elevatie en cumulatieve ST deviatie als voorspellers voor mortaliteit in STEMI patiënten. Daarom hebben we hier onderzoek naar gedaan in een STEMI populatie van 4513 patiënten (**hoofdstuk 8)**. We hebben aangetoond dat de grootte van cumulatieve ST deviatie 30-dagen mortaliteit voorspelt (T1: referentie, T2: OR: 1.09 95% BI (0.67-1.77), T3: OR 1.76 95% BI (1.14-2.73)). De grootte van zowel cumulatieve ST elevatie (T1: referentie, T2: OR: 1.17 95% BI (1.00-1.38), T3: OR: 1.21 95% BI (1.04-1.42)) als cumulatieve ST deviatie (T1: referentie, T2: OR: 1.14 95% BI (0.98-1.34), T3: OR: 1.32 95% BI (1.13-1.53)) voorspelt lange termijn sterfte (mediaan: 7.1 jaar, IQR: 4.7-9.4). Daarom is het van belang dat naast cumulatieve ST elevatie ook de grootte van cumulatieve ST deviatie wordt meegenomen, zodat de voorspellende waarde van het 12 afleidingen ECG vergroot wordt met name voor 30-dagen mortaliteit in STEMI patiënten die gepland zijn om een primaire PCI te ondergaan.

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 10 juli 1984 te Gaasterland. Zij groeide op in het pittoreske dorpje Nijemirdum in het zuidwesten van Friesland. Na het behalen van het eindexamen van het Voortgezet Wetenschappelijk Onderwijs aan het Bogerman te Sneek in 2003, is zij verhuisd naar Utrecht om te studeren aan de Universiteit van Utrecht. In 2006 werd de bachelor van Biomedische Wetenschappen behaald en in 2008 de master van Science Education and Communication. Tijdens het vierde jaar van haar studie maakte Sonja kennis met het klinische wetenschappelijk onderzoek tijdens een onderzoeksstage bij de afdelingen cardiologie en klinische chemie van het St. Antonius ziekenhuis te Nieuwegein. Tijdens het vijfde jaar van haar studie heeft zij stage gelopen bij de Leidsche Rijn Julius Gezondheidscentra te Leidsche Rijn. Eind 2008 volgde een aanstelling als onderzoeksmedewerker en promovendus bij Diagram B.V. in Zwolle. In 2012 werd deze functie verruild voor junior projectcoördinator en per begin 2014 werd Sonja aangesteld als projectcoördinator bij Diagram B.V. Eind 2014 heeft zij de postinitiële masteropleiding Epidemiologie aan de Vrije Universiteit Amsterdam afgerond.

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