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Strategies to improve outcome in patients with ST elevation myocardial infarction treated with primary PCI

Tim Tödt

Division of Cardiovascular Medicine
Department of Medical and Health Sciences
Linköping University, Sweden



Linköping University
FACULTY OF HEALTH SCIENCES

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To my Father who would have loved to see this day!

*Allt kan alltid till slut bli mycket bra.
Wilfrid Stinissen*

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ABSTRACT

Background

ST elevation myocardial infarction (STEMI) caused by a ruptured atherosclerotic plaque with overlying thrombosis leads to ischemia and progressively to the death of the myocardial cells supplied by the affected coronary artery. Rapid reperfusion with primary Percutaneous Coronary Intervention (PCI) in an experienced centre is the preferred therapy for these patients. The aim of the research program on which this thesis is based was to study the effect of antiplatelet therapy with abciximab on coronary patency when administered early to an unselected cohort of patients with STEMI intended for primary PCI, to study the impact of health care delay time on infarct size measured with contrast enhanced Magnetic Resonance Imaging (ceMRI), and to evaluate if time delays could be reduced through reorganisation of logistics and personal feedback to staff involved in the care of STEMI patients. Finally measures of wall motion on cine MRI were evaluated to elucidate if functional measurements of the left ventricular wall could detect scar tissue visualised on ceMRI in a post-acute phase of primary PCI.

Material and results

In **paper I** we report on a study of all consecutive patients who sustained a STEMI in 2005 in the county of Östergötland and who were to be treated with primary PCI. Abciximab given as pre-treatment before (n=133) or at the cath-lab after a diagnostic angiography (n=109) was associated with a patent Infarct Related Artery (IRA), i.e. Thrombolysis in Myocardial Infarction (TIMI) flow 2-3, in 45.9% of patients in the early group versus 20.2% in the cath-lab group, $p=0.0001$. There were no statistically significant differences in bleeding or mortality rate during the initial hospital stay, nor were there any significant differences between the groups during one-year follow up regarding a Major Adverse Cardiac Event (MACE).

Paper II is based on an examination of 30 patients in a stable clinical condition with ceMRI 4-8 weeks after they had been treated with primary PCI because of STEMI. Patients were selected on the presence of extensive myocardial scar in the anteroseptal segments (n=17) or no scar visible at all in this area or in any other part of the myocardium (n=13). The purpose of the study was to evaluate the ability of a new feature tracking software to measure functional parameters of the heart. The left ventricular wall was divided into 18 segments and myocardial contraction was measured with velocity, displacement and strain in the longitudinal and radial direction. The software calculated a

mean value for the 18 segments for each parameter. Receiver-operator-characteristics curves (ROC) were constructed. The best area-under-curve (AUC) was for radial strain where a cut-off value of 38.8% had 80% sensitivity and 86% specificity to detect segments with scar>50%.

The impact of health care delay was examined in **paper III** based on a study in which 89 STEMI patients treated with primary PCI had their infarct size measured with ceMRI in the post-acute phase. Time from First Medical Contact (FMC) to a patent artery correlated weakly with infarct size, $r=0.27$, $p=0.01$. However, multivariable analysis showed the LAD as the Infarct Related Artery (IRA), active smoking and occlusion of the IRA at the time of the diagnostic angiogram were correlated with infarct size and that time from FMC to patent artery was not so correlated.

Finally, in the study leading to **paper IV**, extensive measurements on time delays were performed on 67 consecutive patients with STEMI treated with primary PCI. Through collaboration with different stakeholders in the treatment of STEMI in the catchment area the following types of targeted refining of logistics were done; **1.** Ambulance staff prioritise ECG recording, **2.** Central evaluation of ECG in all patients with suspected STEMI, and **3.** PCI team is ready to accept the patient when two out of three members are on site. Moreover, personal feedback on time delays for each STEMI patient was given to all staff involved in the treatment of the patient. Thereafter, all the time delays for a similar group of consecutive STEMI patients ($n=89$) were analysed and compared with the delays for the former group. Improvements seen in the post-intervention group were a reduction in time from ECG to cath-lab arrival by 11 minutes, $p=0.02$ and a non-significant decrease of FMC to a patent artery by six minutes. The main part of this improvement could probably be ascribed to the decision to see to it that an attending cardiologist was present 24/7 and to central evaluation of ECG.

Conclusion

Abciximab given as pre-treatment to patients with STEMI intended for primary PCI was associated with a patent artery in 46% of patients. Moreover, we demonstrated a relationship between health care delay time and infarct size. This delay time could be reduced by a reorganisation of logistics and personal feedback on time delays. Finally, feature tracking analysis of cine MR images could detect segments with extensive myocardial scar in anterior infarction with 80% sensitivity and 86% specificity.

LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by Roman numerals.

- I Tödt T, Sederholm-Lawesson S, Stenestrand U, Alfredsson J, Janzon M, Swahn E.
Early treatment with abciximab in patients with ST elevation myocardial infarction results in a high rate of normal or near normal blood flow in the infarct related artery.

Acute Cardiac Care, 2010; 12:10-17.
- II Maret E, Tödt T, Brudin L, Nylander E, Swahn E, Ohlsson JL, Engvall JE.
Functional measurements based on feature tracking of cine magnetic resonance images identify left ventricular segments with myocardial scar.

Cardiovascular Ultrasound. 2009 Nov 16; 7:53.
- III Tödt T, Maret E, Alfredsson J, Janzon M, Engvall JE, Swahn E.
Relationship between treatment delay and final infarct size in STEMI patients treated with abciximab and primary PCI.

BMC Cardiovascular Disorders. 2012 Feb 23; 12:9.
- IV Tödt T, Alfredsson J, Swahn E, Janzon M.
Strategies to reduce time delays in patients with acute coronary heart disease treated with primary PCI. The STOP WATCH study.

Submitted.



ABBREVIATIONS

ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
ADMIRAL	Abciximab before Direct Angioplasty and Stenting in Acute Myocardial Infarction Regarding Acute and Long-term Follow up
AHA	American Heart Association
ANOVA	Analysis of Variance
ASA	Acetyl Salicylic Acid
AUC	Area Under the Curve
BRAVE	Bavarian Reperfusion Alternatives Evaluation
B-SSFP TFE	Balanced steady state free precession turbo field-echo
CABG	Coronary Artery Bypass Grafting
CAPTIM	Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction
CCU	Coronary Care Unit
ceMRI	contrast enhanced Magnetic Resonance Imaging
CT	Computed Tomography
ECG	Electrocardiogram
EMS	Emergency Medical System
ESC	European Society of Cardiology
FINESSE	Facilitated Intervention with Enhanced reperfusion Speed to Stop Events
FMC	First Medical Contact
Gd-DPTA	Gadopentetate Dimeglumine
GFR	Glomerular Filtration Rate
GISSI	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico

Gp	Glycoprotein
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HORIZONS-AMI	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction
ICC	Intraclass Correlation Coefficient
ISIS-2	Second International Study of Infarct Survival
IR	Inversion Recovery
IRA	Infarct Related Artery
IR TFE	Inversion Recovery Turbo Field Echo
IQR	Inter Quartile Range
LAD	Left Anterior Descending artery
LGE	Late Gadolinium Enhanced
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Event
MRI	Magnetic Resonance Imaging
PCI	Percutaneous Coronary Intervention
PRAGUE	PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis
RCA	Right Coronary Artery
RF	Radio Frequency
RIKS-HIA	Register of Information and Knowledge about Swedish heart Intensive Care Admissions
ROC	Receiver Operating Characteristics
SSFP	Steady State Free Precession

SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SD	Standard Deviation
STEMI	ST Elevation Myocardial Infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence based care in Heart disease Evaluated According to Recommended Therapies.
TE	Echo Time
TFE	Turbo Field Echo
TIMI	Thrombolysis in Myocardial Infarction
TR	Repetition Time



INTRODUCTION

BACKGROUND

Every year more than 5000 people in Sweden need rapid medical care because of a STEMI ¹. Even though the incidence and case fatality rate have decreased during the past several decades ^{2,3} the consequences regarding mortality, morbidity and cost to the society are serious ⁴. The main focus of the research on which this thesis is based was to provide a foundation for discussing strategies used to improve outcome in patients with STEMI treated with primary PCI. One strategy is adjunctive early antiplatelet therapy with Gp IIb/IIIa inhibitors, i.e. facilitated PCI, with the goal of establishing a patent IRA before coronary intervention. Another strategy is to reduce ischemic time. If we assume a relationship between health care delay time and outcome in STEMI, a hypothesis explored in this thesis, strategies to reduce this delay could be of benefit to the patient.

THE UNDERLYING PATHOLOGY OF STEMI

In 1927, Benson was the first to describe coronary thrombosis due to fissuring of the intima as a cause of acute myocardial infarction ⁵. In 1983 the Danish pathologist Erling Falk demonstrated the primary role of plaque rupture as a trigger of coronary thrombosis ⁶, Figure 1. The thrombus interrupts blood flow distal to the clot consequently resulting in myocardial cell death due to prolonged ischemia ⁷. Fissuring and disruption of atherosclerotic plaques can take place even in non-significant coronary stenosis, Figure 2.

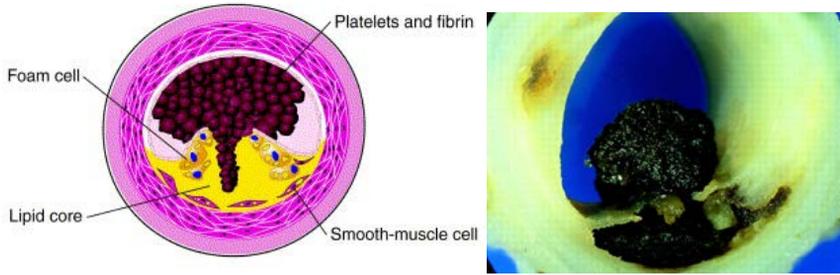


Figure 1. Depicts a human coronary artery showing a ruptured atherosclerotic plaque. Thrombus is filling the plaque and part of the artery. Reprinted with permission from Elsevier (left) and BMJ Publishing group (right).

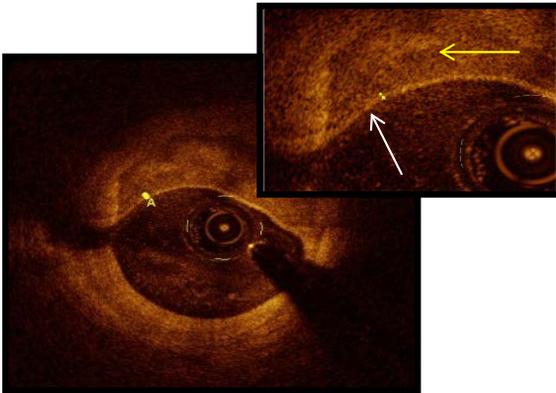


Figure 2. Depicts Optical Coherence Tomography inside the Left Anterior Descending artery of a human being. The white arrow points to a thin capsule overlying an atherosclerotic plaque (yellow arrow). Due to the thin capsule of the plaque the risk of rupture and subsequent occlusive thrombosis is very high. The person succumbed from an anterior myocardial infarction some weeks after the study. Courtesy of Dr. Dario Hauer, Linköping.

Animal ⁸ and clinical studies ⁹ have demonstrated that myocardial cell death occurring over time is spread like a wave front in the myocardium. Myocardial cell death begins as early as 20 minutes after the occlusion of the artery and is said to be complete within six hours, Figure 3. This period can vary considerably due to several factors including the presence of intermittent periods of transient reperfusion, collateral circulation or the presence of ischemic preconditioning ^{10,11}. The loss of

functional myocardium leads to a reduction in left ventricular function, a process that can affect the patients' quality of life and cause premature death¹².

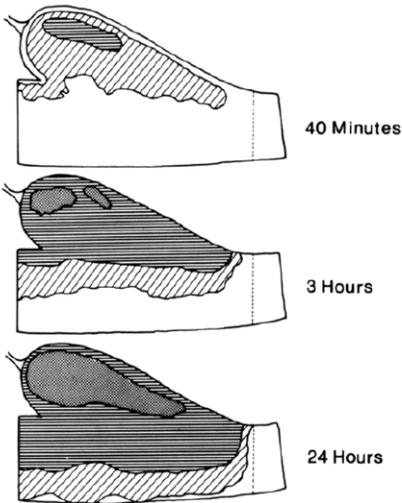


Figure 3. Diagrammatic summary of the progression of ischemia with respect to the duration of the coronary occlusion. Necrosis (all shaded areas) occurs first in the subendocardial area and is spread "like a wave" to involve more and more of the ischemic zone. Microvascular injury (horizontal cross hatching) and the extent of the central necrotic core (dotted areas) also progress from subendocardial to subepicardial zones but the time scale is slower. Reprinted with permission from Wolters Kluwer Health.

THROMBOLYSIS FOR REPERFUSION

In the late 1980s the GISSI 1 and ISIS 2^{13,14} studies found that a comparison of patients with STEMI thrombolytic therapy (Streptokinase) with those given a placebo established that the therapy reduced short term mortality by almost 3%. These results were improved in the GUSTO 1 study in which there was a further reduction of mortality if front-loaded alteplase was used instead of streptokinase¹⁵. Interestingly, a GUSTO 1 angiographic substudy revealed an association between the patency of the IRA and outcome¹⁶. Studies have shown that time to reperfusion with

thrombolysis is a critical determinant of outcome¹⁷. Thrombolytic therapy has its greatest effect on reperfusion when administered to patients within 2-3 h after symptom onset, the so called golden hour¹⁸. Prehospital administration of thrombolytic therapy to STEMI patients has been effective and safe and is associated with substantial gain in time to treatment and efficacy^{19,20}. It seems that the ability of thrombolytic agents to reperfuse the occluded artery diminishes with time^{21,22}.

PERCUTANEOUS CORONARY INTERVENTION

On September 16, 1977, Dr. Andreas Grüntzig performed the first coronary angioplasty on a 38-year-old businessman suffering from angina because of a stenosis on the LAD, Figure 4²³. Later that year at the 50th Scientific Sessions of the AHA, Grüntzig presented four cases treated with coronary angioplasty²⁴. The method became widespread and in 1982 the first PCI in STEMI was performed²⁵.

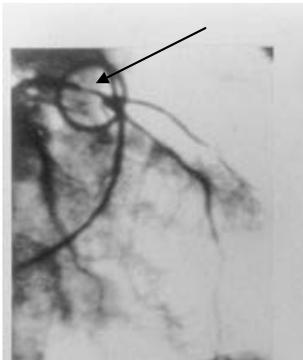


Figure 4. *The angiogram of the first PCI showing a stenosis in the proximal LAD (Arrow). Reprinted with permission from Wolters Kluwer Health.*

In 1993 two randomized studies comparing primary PCI with thrombolysis in STEMI showed a reduction in death or reinfarction²⁶ and a higher patency rate of the IRA and better left ventricular function²⁷ in favour of PCI. The debate about which method of revascularization should be used in this setting became intense²⁸. However, in 2003 Keeley presented a Meta-analysis of 23 randomized

trials²⁹ that showed a 27 % reduction in short-term mortality in patients treated with primary PCI compared to those receiving reperfusion therapy with thrombolysis. The analysis also provided evidence that PCI reduced reinfarction, intracranial bleeding, reocclusion of the IRA and recurrent ischemia. Primary PCI became more and more the preferred method of revascularization in STEMI and is used in more than 80% of patients under the age of 80 with STEMI in Sweden today³⁰, Figure 5. A major drawback with primary PCI is the limited access to hospitals where primary PCI can be performed since primary PCI requires a highly coordinated organization, especially when transfer of patients from hospitals without these facilities is needed to provide PCI at one so equipped³¹.

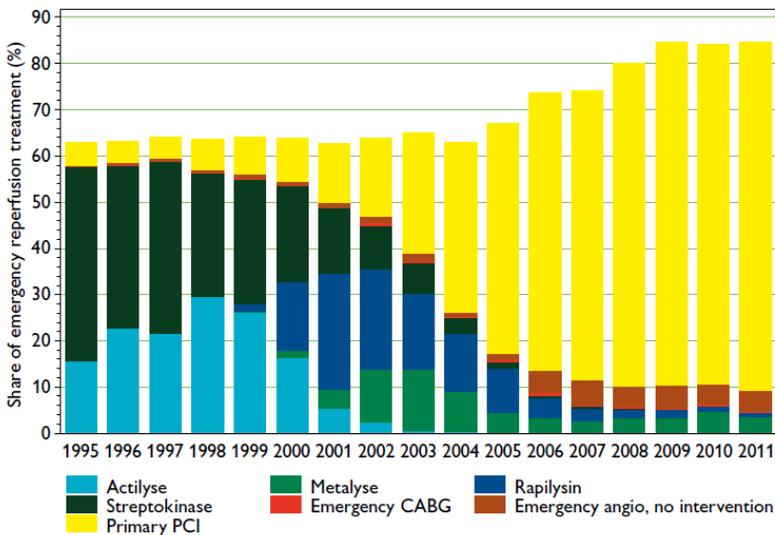


Figure 5. Evolution of reperfusion therapy in patients with STEMI in Sweden. From SWEDEHEART annual report 2011

(English). (<http://www.ucr.uu.se/swedeheart/index.php/arsrapporter>)

TIMELINESS OF REPERFUSION

Given the urgency of reperfusion of the occluded artery, considerable attention has been given to the implementation of a reperfusion strategy that salvages as much myocardium as possible. A fundamental aspect of reperfusion is that time is essential since ischemia leading to myocardial cell death is a progressive process. In a meta-analysis by Nallamotho the PCI related delay beyond which the benefit of primary PCI over thrombolysis was outweighed by the harmful effect of postponing reperfusion therapy was 60 minutes. In other words if PCI was delayed more than 60 minutes in comparison to thrombolysis, the latter should become the preferred reperfusion therapy.³² Other authors have questioned this relatively short PCI-related delay and have argued that the time frame is based on summary statistics rather than individual data³³. A meta-analysis based on individual patient data made by Boersma found a beneficial effect of primary PCI even at PCI-related delays of 80-120 min³⁴. The acceptable delay for PCI in comparison with thrombolysis probably varies according to time from symptom onset, infarct location and the patient's bleeding risk. In a subgroup analysis of the CAPTIM trial³⁵ there was a higher mortality in patients who presented within two hours of symptom onset and had been treated with primary PCI than those receiving pre-hospital thrombolysis. And in the PRAGUE2 trial, thrombolysis given within 3 hours of symptom onset was equal to primary PCI in terms of mortality at 30 days³⁶. The recent guidelines from the ESC recommend that thrombolysis be seen as an alternative to primary PCI when PCI cannot be performed within 120 minutes of the FMC and in patients showing symptoms of short duration, i.e. < 2h³⁷.

DOES TIME MATTER IN PRIMARY PCI?

It has been held that primary PCI may be relatively independent of the time interval between symptom onset, that is the presumed time of the occlusion of the IRA, and mechanical reperfusion

with primary PCI³⁸. Some studies have suggested that time delays in primary PCI are important only within the first 2-3 hours^{39,40} or in high risk patients, such as those in cardiogenic shock⁴¹. Other studies have shown a poorer outcome in STEMI patients with a delay of treatment with PCI⁴²⁻⁴⁵. In contrast there has been more consistency regarding delays in door-to-balloon times and outcome, that is the time the health care system needs to establish reperfusion of the IRA⁴⁶⁻⁴⁸. Door-to-balloon time has become an important issue to be studied and to then be improved⁴⁹⁻⁵³. This time interval is also regarded as an indicator of the quality of the institution delivering primary PCI⁵⁴. Several strategies have been associated with reducing delay time; these include pre-hospital ECG to activate the cath- lab, an attending cardiologist on site 24/7, continuous feedback and interdisciplinary collaboration throughout the process⁵⁵⁻⁵⁷. Multiple studies have evaluated these strategies⁵⁸⁻⁶². However, only a few of the studies have been done in a setting with a high frequency of direct admission by ambulance to the cath lab^{63,64}, a strategy common in Scandinavia and used frequently in our STEMI network. Many hospitals still fail to deliver reperfusion therapy with PCI within a satisfactory time interval; room for improvement exists^{30,65,66}.

FACILITATED PRIMARY PCI

The purpose of facilitated PCI in STEMI is to improve the patency of the IRA by administration of pharmacological substance(s) before the intervention^{67,68}. Gp IIb/IIIa inhibitor therapy has been shown to inhibit platelet aggregation^{69,70} and thrombus formation on damaged endothelium⁷¹ and can dissolve thrombi already formed⁷². The effects of this process can be observed within 10 minutes after initiation of therapy⁷³. Antiplatelet therapy with Gp IIb/IIIa inhibitors has been associated with improved outcome when given as adjunctive therapy to primary PCI⁷⁴⁻⁷⁷ especially in high risk patients^{78,79}. Results from the ADMIRAL⁸⁰ trial indicated that early administration was associated with an amplification of the treatment effect⁸¹. Furthermore, patients who had already received Gp IIb/IIIa inhibitor therapy in the Emergency Room had an enhancement of TIMI flow

before intervention, a finding corroborated by several trials⁸²⁻⁸⁷. A strategy of giving antiplatelet therapy with Gp IIb/IIIa inhibitors as early as possible has been examined in several studies and has been associated with smaller infarct size⁸⁸, improved left ventricular function⁸⁹, lower risk of heart failure⁹⁰, better ST-segment resolution after intervention^{91,92}, higher degree of myocardial salvage^{93,94}, aborted myocardial infarction⁹⁵, and lower mortality⁹⁶⁻⁹⁹, especially among high risk patients¹⁰⁰. However other studies have not been able to show these beneficial effects among STEMI patients treated with primary PCI¹⁰¹⁻¹⁰³. Moreover, studies of the clinical effects of early Gp IIb/IIIa blockade on top of a high loading dose of clopidogrel (600 mg) have shown conflicting results^{92,104-106}.

The randomised FINESSE study including almost 2500 patients could not show improved clinical outcome with a strategy that used facilitation with the Gp IIb/IIIa inhibitor abciximab¹⁰⁷. However, a substudy of that trial showed a benefit in the primary endpoint in high risk patients¹⁰⁸. Recently in the large scale HORIZON-AMI study it was reported that there was a significantly higher rate of major bleeding and a worse net clinical outcome in patients treated with Gp IIb/IIIa inhibitors in comparison with those treated with the direct thrombin inhibitor bivalirudin¹⁰⁹. Guidelines from the ACC/AHA state that the results of the studies with Gp IIb/IIIa inhibitors cited above are inconclusive now in an era where patients receive dual-antiplatelet therapy together with heparin or bivalirudin. The adjunctive use of Gp IIb/IIIa inhibitors can be useful in primary PCI but is not recommended as routine therapy¹¹⁰. The recent guidelines from the ESC conclude that the desirability of using upstream Gp IIb/IIIa blockade is uncertain³⁷.

CONTRAST ENHANCED MAGNETIC RESONANCE IMAGING

The basic principle of MRI is the excitation of the hydrogen nuclei by external RF to create tissue magnetization that decays (relaxation). Hydrogen is abundant in water and fat. In its resting state hydrogen nuclei spin randomly either parallel or anti-parallel (a few) to the magnetic field. The RF pulse excites the nuclei that now spin in a different plane, off angle to the magnetic main field. When the RF pulse is turned off the nuclei return to their basal state. This process releases energy that can be transformed into a radio signal and further transformed to an image. Relaxation is quantified as T1 signal (transverse axis) and T2 (return of the signal in the longitudinal axis). The properties of the signals are specific for different tissues allowing differentiation between blood, epicardial fat, cardiac muscle and myocardial scar ¹¹¹. Gradient echo images and SSFP sequences are commonly used and have remarkable contrast. Protocols used today have a high signal to noise ratio and high spatial resolution ¹¹². Cine MRI allows for assessment of regional wall motion which also can be done during stress with dobutamine. Gadolinium is a chemical element that has paramagnetic properties. It has been used ubiquitously in MRI of the entire body and was pioneered in studies of myocardial infarction by Kim et al. ¹¹³. Gadolinium rapidly distributes into interstitial areas of the myocardium and accumulates in the scar tissue because of a delayed wash out. It shortens the T1 relaxation producing a bright, white signal that distinguishes scarred from normal myocardium, Figure 6 ¹¹⁴. This technique, known as Late Gadolinium Enhancement or ceMRI, has become a powerful tool for measuring relative as well as absolute infarct size after myocardial infarction ¹¹⁵⁻¹¹⁷. Using this technique the region and size of the irreversibly damaged myocardium can be identified accurately and can be quantified ¹¹⁸⁻¹²¹.



Figure 6. ceMRI depicting large anterior myocardial infarction (Arrows). Gadolinium is enhanced in scarred tissue and shortens relaxation time more in the infarct than in normal tissue giving a bright, white signal clearly delineating the infarct from the normal tissue. Courtesy of Dr. Jan Engvall, Linköping.

Moreover, transmuralty of the infarct in excess of 50% of the myocardial wall thickness has been associated with a negative predictive value of 90% of absence of functional recovery after revascularisation¹²². Concern has been raised regarding the rare but feared complication called nephrogenic systemic fibrosis that can be induced by the administration of gadolinium contrast to patients with renal insufficiency (GFR < 30 ml/min). Reduction in glomerular filtration rate carries a worse prognosis among patients with STEMI¹²³ especially in women¹²⁴. Recent work has shown a worse prognosis in patients with STEMI even with mild impairment of renal function¹²⁵. If possible, gadolinium contrast should not be given to patients with reduced kidney function¹²⁶. If other MRI methods could be used in STEMI to evaluate myocardial function and infarct size without the necessity of using gadolinium contrast this could possibly be of benefit for the patient.

THE STEMI NETWORK IN ÖSTERGÖTLAND, SWEDEN

On January 1, 2005, the Department of Cardiology at the University Hospital, Linköping, adopted a strategy of primary PCI for all patients in the county of Östergötland (420 000 inhabitants) if there was reason to suspect the presence of an acutely occluded coronary artery. Patients presenting with symptoms suggestive of acute coronary syndrome and ECG signs of transmural ischemia, i.e. ST

elevation, extensive anterior ST depression or presumed new bundle branch block, were sent directly to the cath-lab for planned primary PCI. Patients were pre-treated with aspirin 300 mg orally if there was no contraindication. Abciximab bolus (0.25 mg/kg), Heparin 50 E/kg, maximum 5000 E, and betablockers were all given at the discretion of the attending physician. Physicians were encouraged to pre-treat the patient with abciximab if the patient had clear symptoms of an ACS and distinct signs of ischemia on the ECG. On the other hand, patients with a high risk of bleeding, i.e. patients on warfarin, who were older, who had a history of bleeding or for whom the diagnosis was unclear were recommended to receive abciximab, if at all, first after a diagnostic angiogram had confirmed an occlusion/stenosis in the IRA and that the obstruction was suitable for PCI. A clopidogrel loading dose of 375 mg was given to all patients without a contraindication in the CCU after angiography/PCI had been carried out unless the patient was scheduled for CABG in the following days. Based on the results of the FINESSE ¹⁰⁷ and HORIZONS-AMI ¹⁰⁹ trials, Gp IIb/IIIa inhibitors are at the moment not given as pre-treatment by the EMS in the county of Östergötland. However, in rare cases they are given in the Emergency Room of the admitting spoke hospitals in Motala and Norrköping while waiting for transfer of the patient to the cath-lab at the University Hospital in Linköping.



AIMS

The aims of the research program on which this thesis is based were to

- study the effect of the early administration of antiplatelet therapy on coronary patency and major adverse cardiovascular events in an unselected cohort of consecutive patients with ST elevation myocardial infarction planned for primary PCI.
- study the impact of health-care delay in patients with STEMI on infarct size measured with cardiac MRI.
- In the post-acute phase evaluate measures of wall motion on cine magnetic resonance images in patients with STEMI treated with primary PCI to elucidate if functional measurements of the left ventricular wall could detect scar defined with gadolinium contrast enhanced MRI thus avoiding the use of intravenous gadolinium contrast.
- identify points of time delays in the STEMI network in Östergötland, Sweden, between first medical contact and establishment of a patent infarct related artery in order to
- reduce time delays through reorganization of logistics and personal feedback to staff involved in the care of STEMI patients.



MATERIAL AND METHODS

PAPER I

In the study for paper I all patients with a STEMI intended for primary PCI at the University Hospital in Linköping were considered for the “STEMI 2005” study. Between 1 st January and 31 st December 2005 all admitted patients were logged on a log sheet in the CCU at the University Hospital regarding key information on time of symptom onset, ECG findings, time of administration of abciximab bolus and time of arrival at the cath-lab.

In addition patients were registered in the quality databases RIKS-HIA ¹²⁷ and SCAAR ¹²⁸ . RIKS-HIA contains information about patients admitted to CCU of the participating hospitals in Sweden while SCAAR holds information on coronary angiography/PCI procedures performed in cath-labs in Sweden including complications from the procedure. From RIKS-HIA information on demographic data, risk factors, ECG, Killip class on admission and type of medical treatment was obtained. The SCAAR registry was used to retrieve data on type of stent uses, lesion location, renal function and information on major and minor bleeding after PCI. The registries are repeatedly merged with information from the National Cause of Death Register.

All angiograms were analysed by three experienced PCI operators to identify the IRA, the location of the culprit lesion, TIMI flow grade before and after PCI, type of PCI performed and if treatment had been successful (defined as obtained TIMI 3 flow and stenosis of the culprit lesion < 50%). Reinfarction during the initial hospital stay was defined as a new rise in in myocardial markers with at least 50 % accompanied by new ischaemic symptoms. After discharge reinfarction was defined as rehospitalisation with a diagnosis at discharge of myocardial infarction or myocardial infarction

verified by autopsy. Major bleeding was defined as intracranial bleeding (confirmed by CT scan), or other bleedings accompanied with a reduction in haemoglobin of > 50 g/l. Minor bleedings were defined as a fall in haemoglobin between 30 and 50 g/l or unobserved bleeding with a fall in haemoglobin between 40 and 50 g/l. A pseudoaneurysm requiring surgery, local injection of thrombin or ultrasound guided local compression was also considered a minor bleeding. RIKS-HIA was used to verify if the patient had a new myocardial infarction or had died after the index hospitalisation.

The Swedish Registry Heart Surgery in Adults and Children and the local cardiac database at the Heart Centre, Östergötland, was used to identify patients with a CABG surgery after the index myocardial infarction. The SCAAR registry was used to examine if the patient underwent repeat angiography or PCI and all new angiograms and procedures performed at the cath-lab at the Department of Cardiology, Linköping, were scrutinized for the presence of a new lesion, restenosis or stent thrombosis after the index procedure, and any new procedure performed. In doubtful cases the patient's medical records were used for clarification.

A MACE was defined as death, non-fatal reinfarction or a revascularisation not planned at the index procedure. Patients were followed for one year regarding myocardial infarction and revascularisation. Mortality status was followed for two years. The cause of death was available only until December 2006.

PAPER II

Between February 2006 and September 2007, 99 patients treated with primary PCI at the cath-lab at the University Hospital in Linköping were examined with ceMRI six weeks after their infarction in a study that evaluated the impact of health care delay time on infarct size. From this population we selected 30 patients to study a new feature tracking software (At the time called Diogenes MRI, now available as 2D-CPA, Tomtec GmbH, Unterschleissheim, Germany) on cine MRI to evaluate the capacity of the software to measure functional parameters of the left ventricular myocardium and thereby detect the segmental distribution of infarcted myocardium. If use of such software was successful, the administration of intravenous gadolinium contrast could possibly be avoided since it has been associated with nephrogenic systemic fibrosis, especially in patients with reduced kidney function.

The 30 patients were selected on the presence or absence of extensive myocardial scar in the anterior or anteroseptal segments that were considered to belong to the LAD territory. Scar patients (n=17) were defined as having a scar area in excess of 75 % in at least one segment belonging to this area. Non-scar patients had no visible scar in this area, or in any other part of the myocardium. These patients did not display scar on ceMRI despite unequivocal signs of STEMI necessitating PCI of a clear culprit lesion and having been discharged with a diagnosis of myocardial infarction. The anteroseptal area was selected because it was the most frequent infarct location in the study population. The intention was to contrast the possible effects of a scar on the functional parameters that were to be determined with the feature tracking software.

Cine short axis loops were used to determine left ventricular volumes, mass and ejection fraction. Contrast enhanced images were acquired at the same slice positions as the cine images about 20

minutes after administrating gadopentetatedimeglumine 0.2 mmol/kg bodyweight (Schering Nordiska AB, Järfälla, Sweden). The size of the scar was determined in ml and as percentage of left ventricular mass using “Segment”, a freely available software (<http://www.medviso.com/segment>). In this study, transmuralty was defined as infarct area divided by segment area, Figure 7.

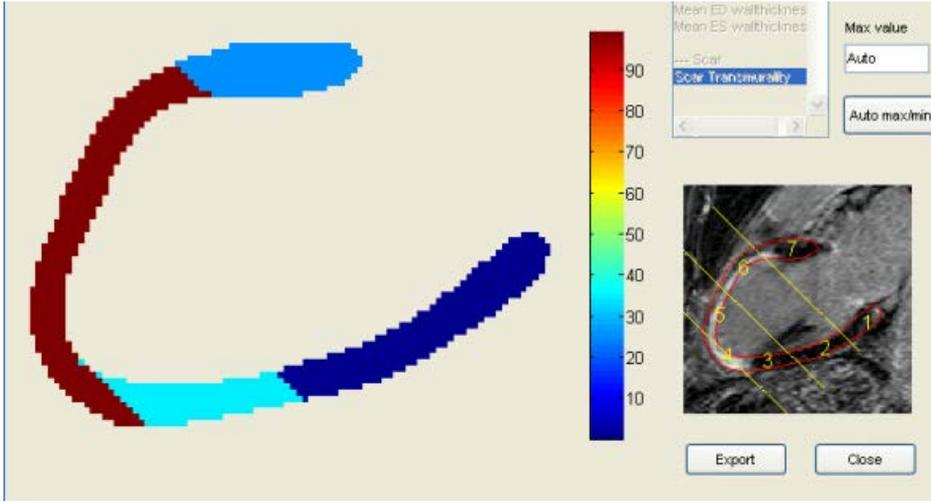


Figure 7. Transmuralty of scar calculated from Late Gadolinium Enhanced image (2 chamber view). Scar is 100 % transmural along the middle and apical part of the anterior wall. Calculation performed with the “Segment” software. Reprinted with permission from *Cardiovascular Ultrasound*.

The feature tracking software utilizes principles of pattern recognition well known from other areas of image analysis. Briefly, the left ventricle is manually segmented along the endocardial border. The software scans perpendicularly to the endocardial outline and starts with a distance of 1/16 of the endocardial perimeter, reducing the distance with successive iterations. Based on tracking particular features of the myocardium, velocity, displacement and strain can be calculated in the radial as well as in the longitudinal and circumferential direction, Figure 8. In this paper, feature tracking was performed on three longaxis cine-loops. The left ventricular wall was divided into 18 segments and the software calculated a mean value for each of the 18 segments for each parameter, Figure 9.

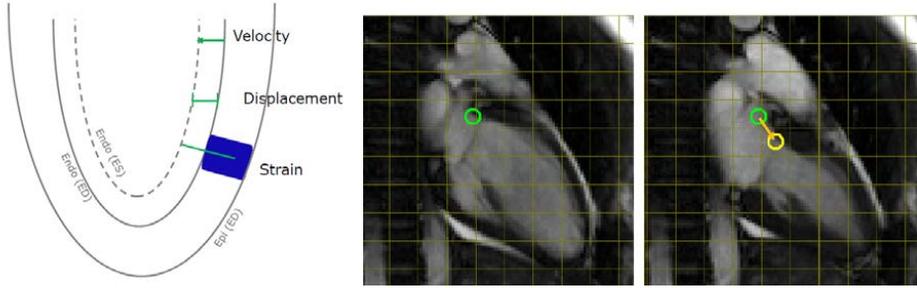


Figure 8. The feature tracking technique uses pattern recognition derived from image processing. Briefly, areas along the endocardial border are scanned for image features that can be followed over time. Successive scans are repeated and refined, starting with a radial distance 1/16 of the endocardial perimeter. The identified points are used for calculating distance, velocity and strain. Courtesy of Rolf Baumann, Tomtec, GmbHUnterschleissheim, Germany.

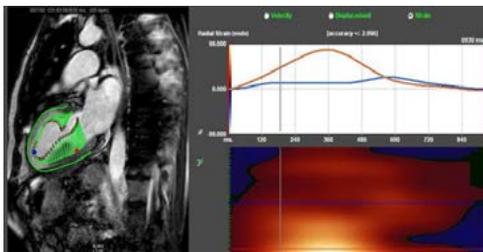


Figure 9. Depicts feature tracking of patient with extensive anterior infarct. Upper right shows radial strain for the entire cardiac cycle. Blue represents the apex showing very low strain values. Red line is the normal posterior wall. Lower right shows radial strain along the entire perimeter in a "colour M-mode" presentation with the posterior position located at the base of the image.

PAPER III

Between February 2006 and September 2007, 589 patients were treated with primary PCI because of ST elevation myocardial infarction at the Department of Cardiology, Linköping. Of these 589 patients, 149 gave their written informed consent to be examined with contrast enhanced Magnetic Resonance Imaging (ceMRI) 4-8 weeks after their index myocardial infarction. Thus, the majority of

STEMI patients were not asked to participate mostly due to administrative reasons, long distance to the hospital, early transfer to the local hospital, or other factors preventing participation of the patient.

After written informed consent had been obtained almost one third of patients (n=60) were excluded due to the following reasons; previous myocardial infarction (7), death (3), reinfarction (1), new revascularisation with PCI/CABG before ceMRI could be performed (15), a new contraindication to ceMRI (3), claustrophobia while in the magnet (4), inability to perform the whole ceMRI study (2), and unwillingness to return to the hospital to perform the ceMRI study (23). One patient was not examined with ceMRI because of malignancy and one patient was lost to follow up. Thus, 89 patients remained for further analysis.

ceMRI was performed 4-8 weeks after the date of primary PCI. The patients were placed in the magnet (1.5 T Achieva, Philips Healthcare, Best, the Netherlands) in supine position. A circular polarized body-array surface coil was used in all measurements. ECG-triggered MR images were obtained during repeated breath-holds. Cine-loops were acquired with a b-SSFP TFE sequence, on average 18, (range 10-23) short axis slices and three long axis planes (apical 2-, 3- and 4-chamber views). Temporal resolution was between 26-41 ms (30 acquired phases). The IR-TFE sequence was a segmented 3D spoiled gradient echo sequence with TE = 1.3 ms, TR = 4.4 ms and TFE factor 43, leading to an acquisition phase time of 188 ms during diastole. Slice thickness was 10 mm, intersection gap -5 mm (i.e. slices were overcontiguous), field-of-view 350 mm and image matrix 128 × 256. The contrast-enhanced images were acquired at the same slice positions as the cine-images, about 20 minutes after the administration of Gd-DTPA 0.2 mmol/kg bodyweight (Schering Nordiska AB, Järfälla, Sweden). Optimal contrast between hyper enhanced areas and normal myocardium was maintained by continually adjusting the inversion time to null the signal from healthy myocardium. Scar size was measured by two different observers on short-axis images using the freely available

software “Segment” <http://segment.heiberg.se>. Infarct volume and percentage was calculated from the short axis stack of slices. End diastolic myocardial and cavity volumes were measured from the short axis LGE images.

All angiograms were reviewed by three experienced PCI operators who were blinded for all other parts of the study. The following items were entered into the database: Infarct related artery, TIMI flow before and after the procedure, type of procedure performed, success of treatment (defined as TIMI 3 flow at the end of the procedure and remaining stenosis < 50 %) and extent of coronary disease. Disagreement was solved by consensus. The different time points were retrieved from clinical records including the EMS report. A TIMI 2-3 flow was regarded as a patent artery. In patients with a TIMI 2-3 flow at the first angiogram this was documented as the time of a patent artery. In patients with an occluded artery at the diagnostic angiogram, i.e. TIMI 0-1 flow, the time of first balloon inflation or activation of a thrombectomy device was considered as the time for a patent artery.

For patients admitted directly to the cath-lab from the ambulance, the time when the patient called the EMS was defined as FMC. For all other patients time of arrival at the Emergency Department was considered as FMC. Patients were followed prospectively for one year for the occurrence of rehospitalisation for angina, myocardial infarction, PCI, CABG and death.

PAPER IV

Between 25 November 2006 and 14 march 2007 we measured multiple time points for patients admitted to the cath-lab at the Department of Cardiology, Linköping for primary PCI because of STEMI. To be included in the study patients had to have:

- ST elevation, extensive anterior ST depression or bundle branch block on the ECG
- Final diagnosis of myocardial infarction (i21 to i23, ICD 10)
- Symptom onset outside of hospital
- Treated with primary PCI at our cath-lab

Patient delay was defined as time from onset of symptoms to FMC. FMC was defined as the time when the patient made contact with the EMS for those who were admitted directly to the cath-lab by ambulance and for all other patients as the time when the patient arrived at the Emergency Department at the respective hospital. Time to decision was defined as time from diagnostic ECG recording to the time when the cardiologist on call decided to proceed with emergency angiographic evaluation of the coronary arteries. Cath-lab time was the time spent from arrival at the cath-lab to balloon inflation, activation of a thrombectomy device or notification of a TIMI 2-3 flow of the IRA, i.e. a patent artery, whichever came first.

Through collaboration with different stakeholders in the treatment of STEMI patients in the county of Östergötland, we made targeted refining of logistics;

- EMS personnel prioritize ECG recording
- Central evaluation of ECG at the CCU at the Department of Cardiology, Linköping, in all patients with suspected STEMI in the county of Östergötland
- PCI team is ready to accept the patient and start the procedure when two out of three members are on site.

After a “wash in period” we again measured relevant time points in a similar cohort of consecutive patients with STEMI to compare the time delays for this cohort with time delays for the initial patient cohort.

ETHICAL CONSIDERATIONS

All studies were approved by the Ethical review boards in Linköping and Uppsala and adhered to the Declaration of Helsinki. Written informed consent was obtained for patients in the studies for papers II and III. Written informed consent was not judged to be possible in the study of the 2005 STEMI population (Paper I), which was a retrospective study and was seen as not being necessary in the STOP WATCH study (Paper IV) where we only recorded time points most of which were in any case recorded in the clinical setting. Moreover, no intervention was done to individual patients, only refining the logistics of the STEMI network organization. The collection of data from RIKS-HIA, SCAAR and the Swedish Registry Heart Surgery in Adults and Children registry was approved by the Swedish Data Inspection Board. Likewise the process of merging RIKS-HIA with the National Cause of Death Register has been approved by the Data Inspection board.



STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS 16.0 - 20.0 (SPSS Inc., Chicago, Illinois, USA) as well as Statistica 8.0 (Statsoft Inc, Tulsa, Oklahoma, USA). Continuous variables were reported as mean +/- SD or median (25th – 75th percentile) as appropriate. For normally distributed variables two-tailed Student's t-test was used to test whether differences between groups were statistically significant. Non-normally distributed variables were compared using the Mann-Whitney U test.

Categorical variables were expressed as counts (percentage). Statistical significance was assessed with the Chi Square or the Fischer's exact test. In paper II ANOVA followed by Duncan's test in case of significance was used when appropriate. Pearson correlation coefficient was used for correlation between global functional measurements and MR- determined LVEF in Paper II. In paper III Spearman correlations were computed for health care related delay time and infarct size.

Receiver -operator-characteristics (ROC) curve analyses were performed using the statistical program MedCalc® Version 6.10 (MedCalc Software, Mariakerke, Belgium). Intra-and interobserver variability of the functional measures was expressed as standard error of a single determination (Smethod) using the formula first proposed by Dahlberg. Smethod was also expressed as % over all means. Single measure intraclass correlation coefficient (ICC) was also used to express interobserver variability. ICC assesses rating reliability by comparing the variability of different ratings of the same subject with the total variation across all ratings and all subjects^{129,130}.

In Paper III multiple linear regression analysis was used to determine independent correlates of infarct size. Variables included in the model were age, sex, active smoker, kidney function, diabetes,

LAD as the culprit artery, an occluded artery on the diagnostic angiogram and time from FMC to a patent artery. Variables were entered simultaneously into the model.

All reported values are two sided. P – values < 0.05 were considered statistically significant.

RESULTS

PAPER I

In 2005 there were 274 patients who suffered an ST elevation myocardial infarction in Östergötland county and were treated with primary PCI at the cath-lab at the University Hospital of Linköping. Of this total, 242 received the Gp IIb/IIIa inhibitor abciximab either as pre-treatment on their way to the cath-lab (early group) or after a diagnostic angiography revealed a stenosis suitable for PCI (cath-lab group). The decision to give abciximab as pre-treatment or immediately before PCI in the cath-lab was left to the attending physician.

The patients in the early group (n=133) compared to late arrivals were more likely to have recorded a pre-hospital ECG, to have been admitted to a spoke hospital and seemed to have more frequent ST elevation on their qualifying ECG. Patients in the cath-lab group more often were given treatment with diuretics on admission and were more frequently discharged with warfarin. The patients' mean age was 65.1 (SD 12) years. Among the 242 patients, 83 (34%) were women, 76 (32%) current smokers, 99 (41%) treated for hypertension, and 43 (18%) had diabetes with no differences between the early and the cath-lab group regarding these markers of cardiovascular risks. Admission directly from ambulance to the cath-lab, by-passing the emergency department, was noted for 111 (46%) patients. The majority of patients presented during off-hours, n=147 (61%).

The median time from symptom onset to a diagnostic ECG was 119 (58-234 IQR) minutes and from ECG to PCI 109 (80-135 IQR) minutes. Patients in the early group received abciximab 75 (61-94 IQR) minutes before PCI, the corresponding time for the cath-lab group was 7 (4-12 IQR) minutes, p=0.0001, Table 1. Patients in the early group had a significantly higher TIMI flow in the IRA at the

first angiogram, Figure 10. There was no difference between the early group and the cath-lab group regarding extent of coronary disease, IRA, complexity of the culprit lesion, frequency of stenting, success of PCI or TIMI flow after PCI.

Table 1.

	Early group (n=133)	Cath lab group (n=109)	P value
Age, years (SD)	65.4 (11.2)	64.8 (12.6)	0.72
Women	42 (31.6)	41 (37.6)	0.32
Diabetes Mellitus	22 (16.5)	21(19.3)	0.58
Hypertension	55 (41.4)	44 (41.1)	0.97
Current smoker	42 (31.8)	34 (31.5)	0.96
Previous myocardial infarction	20 (15.0)	19 (17.4)	0.61
Previous PCI	17 (12.8)	19 (17.4)	0.31
Diuretics on admission	18 (13.5)	26 (23.9)	0.04
Direct admission to PCI lab	66 (49.6)	45 (41.3)	0.20
Admission to spoke hospital	49 (36.8)	24 (22.0)	0.01
Presentation off hours	81 (60.9)	66 (60.6)	0.96
Prehospital ECG	85 (63.9)	49 (45.0)	0.003
ST elevation on diagnostic ECG	127 (95.5)	98(89.9)	0.09
Symptom to ECG, minutes as medians (IQR)	140 (70-230)	111 (46-249)	0.25
ECG to PCI, minutes as medians (IQR)	110 (92-133)	103 (61-144)	0.24

Data are presented as counts (percentage) if not otherwise indicated. SD, Standard Deviation. PCI, Percutaneous Coronary Intervention. IQR, Inter Quartile Range.

After primary PCI and during the initial hospital phase nine (3.7%) patients had died, all due to cardiogenic shock/multiorgan failure. There was no excessive bleeding among patients in the early group. One year after the index myocardial infarction a Major Adverse Cardiac Event (MACE) had occurred in 23% of the patients, most commonly an unplanned revascularization with PCI. The 1-year mortality rate in the patients under study was 7.8% with no significant difference between the groups.

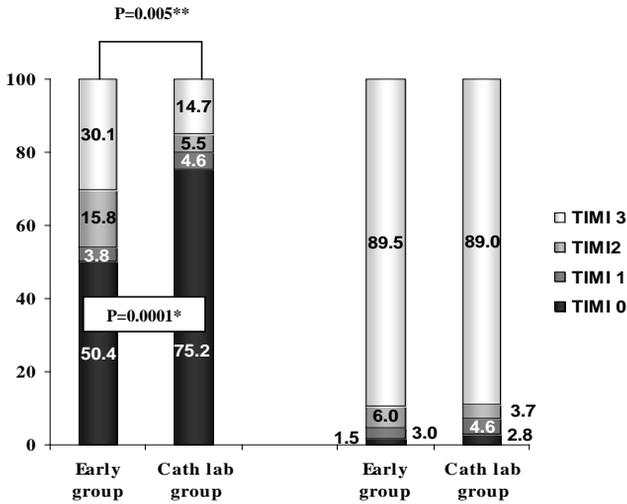


Figure 10. TIMI flow in infarct related artery at first (left) and final (right) angiogram. Numbers are percent of patients with TIMI 0-3 flow. Statistical significance between early and cath-lab group in TIMI 0* and TIMI 3** flow at first angiogram.

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PAPER II

Patients were selected because they had extensive scar in anteroseptal segments (“scar patients”) or no scar at all (“no scar patients”). In scar patients the average scar size was 31 +/- 12 ml which corresponded to 17 +/- 8 % of the left ventricular myocardium. According to literature, patients with a relative scar size larger than 12 % have an unfavourable prognosis¹³¹. In the scar group the scar area was 52 +/- 39% in the anteroseptal segments while no significant gadolinium uptake was seen in patients in the non-scar group. Measures of velocity, displacement and strain were compared between groups. Segments with a scar area exceeding 50 % had significantly lower radial measures on the basis of feature tracking analysis in comparison with segments from patients without scar, Figure 11. Longitudinal velocity and displacement showed less difference possibly due to difficulties in having the software successfully track longitudinal motion. ROC curves were constructed for all measurements for the detection of segments with scar area >50 % since those segments rarely

regain normal function after revascularisation. Radial strain had the highest AUC which means that this measure was best in accurately identifying segments with a large scar. A cut off value of < 38.8% could detect a segment with scar area > 50 % in anteroseptal segments with a sensitivity of 80 % and a specificity of 86 %, Figure 12.

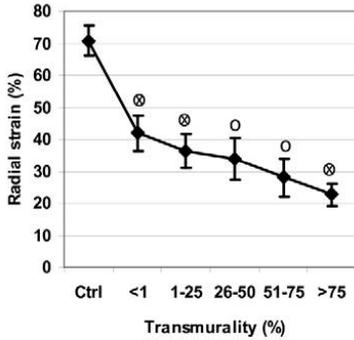


Figure 11. Shown are functional measures vs. transmuralty in all patients. Ctrl = non-scar group. Radial strain in segments is plotted versus segments with various transmuralty. o = statistically significant difference ($p < 0.05$) compared to controls. x = statistically significant difference ($p < 0.05$) compared to nearest left value. Reprinted with permission from Cardiovascular Ultrasound.

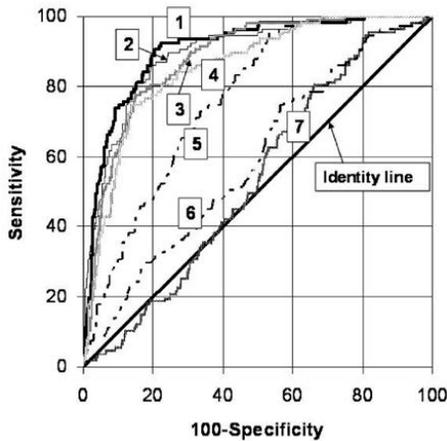


Figure 12. ROC curves for the functional measures vs > 50 % transmuralty on ceMRI. 1=Composite, 2=Radial strain, 3=Radial displacement, 4=Radial velocity, 5= Longitudinal strain, 6=Longitudinal velocity, 7=Longitudinal displacement. Reprinted with permission from Cardiovascular Ultrasound.

PAPER III

The mean age of the 89 patients with STEMI was 62 years (SD 9.7). Only 16% were women and all but one received adjunctive abciximab, 79 % as pre-treatment before diagnostic angiography. Regarding cardiovascular risk factors, almost half of the patients were active smokers, one third received treatment for hypertension on admission but few had been treated for hyperlipidaemia or had been diagnosed with diabetes. A majority of patients (88%) were admitted directly from the ambulance to the cath-lab. The median time from FMC to a patent artery was 89 minutes. The LAD was most frequently the IRA (46%), then the RCA (42%) and lastly the Cx (12%). A patent artery, defined as TIMI 2-3 flow on the initial angiogram of the IRA, was found in 37% of patients. ceMRI was performed within 42 days (range 27-65) after the index infarction.

There was a weak correlation between time from FMC to a patent IRA and infarct size, Figure 13.

Patients with shorter health care delay time, that is FMC to a patent IRA less than 90 minutes, tended to have smaller infarct size 6 ml (1-18 IQR) than those with health care delay times longer than 90 minutes, 12 ml (6-19 IQR), $p=0.07$.

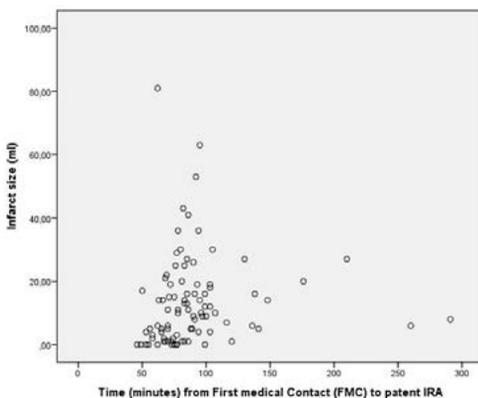


Figure 13. Relationship between time (minutes) from First Medical Contact (FMC) to a patent Infarct Related Artery (IRA) and absolute infarct size (ml). $r=0.27$, $p=0.01$. Reprinted with permission from BMC Cardiovascular Disorders.

Ten patients with no detectable scar on ceMRI but with a clear clinical syndrome of STEMI that was treated with primary PCI had a median delay time of 68 min (52-77 IQR). Using multiple regression analyses LAD as the IRA, active smoking and an IRA with TIMI 0-1 flow at presentation, but not time from FMC to a patent artery, correlated with infarct size.

PAPER IV

During almost five months we did extensive measurements on the time delays affecting consecutive STEMI patients (n=67) treated with primary PCI at the cath-lab at the University Hospital, Linköping. After refining of logistics and continuous feedback on time delays to staff involved in the care of the patients with STEMI another group of consecutive STEMI patients (n=89) was analysed between 1 October 2010 and 17 February 2011 in a similar manner. The former group constituted the pre-intervention group, the latter the post-intervention group. Regardless of the ongoing study the board of the Heart Centre, Linköping, decided to finance an attending cardiologist on site 24/7 from 13 January 2007, which facilitated quick processing of patients with suspected STEMI. The mean age of the patients in the study was 67 years. One third were women. Two thirds of patients were admitted directly by ambulance to the cath-lab. There were no statistical significant differences in baseline characteristics or in IRA between the pre- and post-intervention groups. In the pre-intervention phase more patients were pre-treated with abciximab than during the post-intervention phase, 75% vs 50 %, $p=0.001$. This was probably a consequence of the results published in the FINESSE study¹⁰⁹. There was a trend towards a more frequent presence of patent arteries in the group with a higher frequency of treatment with abciximab before arrival at the cath-lab. No patient was treated with PCI by the radial route in the first phase while 60 % of patients were handled this way in the second phase of the study, $p=0.0005$. The health care delay time decreased from 110 to 104 minutes and time from FMC to cath-lab arrival from 84 to 72 minutes. Furthermore there was a six minute significant reduction from diagnosis of STEMI to decision to proceed with primary PCI ($p=0.004$) and

11 minute reduction from diagnosis to arrival at the cath-lab, $p=0.02$. On the other hand there was a lengthening of time from arrival at the cath-lab to a patent artery by two minutes, $p=0.06$. Figure 14 and Table 2.

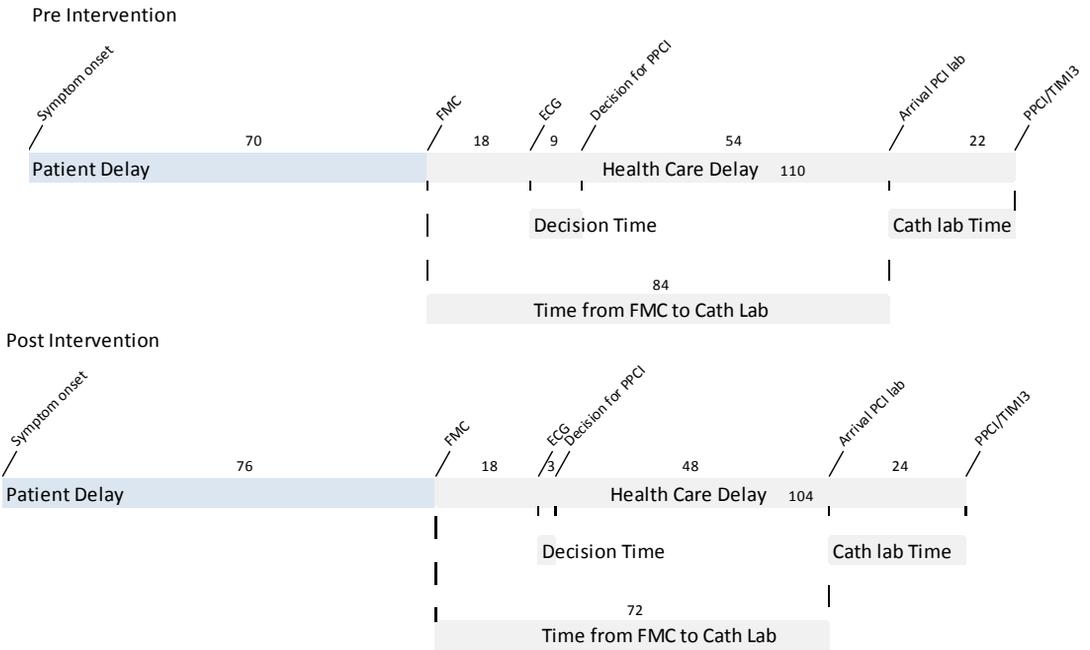


Figure 14. Delays from symptom onset to primary Percutaneous Coronary Intervention in patients with ST-segment elevation myocardial infarction. Numbers indicate median time (minutes). FMC, First Medical Contact. PPCI, Primary Percutaneous Coronary Intervention. TIMI3, Thrombolysis In Myocardial Infarction grade 3 coronary flow, i.e normal flow.

Table 2.

	Pre Intervention N=(67)	Post Intervention N=(89)	P value
Time delays, median, minutes (IQR)			
Symptom to FMC	70 (32-173)	76 (34-154)	0.77
FMC to ECG	18 (10-28)	18 (11-30)	0.85
Ambulance arrival to departure from pt.	20(12-30)	17 (13-22)	0.18
FMC to cath lab	84 (68-115)	72 (62-102)	0.07
FMC to balloon	112 (98-148)	108 (91-150)	0.41
FMC to balloon or TIMI 2-3	110 (95-141)	104 (86-138)	0.30
ECG to decision for primary PCI	9 (2-16)	3 (1-8)	0.004
ECG to cath lab	66 (53-85)	55 (43-70)	0.02
ECG to balloon	96 (82-118)	90 (76-116)	0.28
ECG to balloon or TIMI 2- 3	95 (76-114)	84 (68-110)	0.19
Arrival at cath lab to balloon	28 (22-35)	32 (24-42)	0.03
Arrival at cath lab to balloon or TIMI 2-3	22 (17-30)	24 (19-34)	0.06

Key time measurements. Data are presented as median time in minutes. IQR, Interquartile range. FMC, First Medical Contact. Pt., patient. PCI, Percutaneous coronary intervention. TIMI, Thrombolysis In Myocardial Infarction. TIMI 2-3 flow is defined as a patent coronary artery.

DISCUSSION

There is mounting evidence from clinical trials that primary PCI is the preferred reperfusion strategy in patients with STEMI. The organisation of STEMI networks to facilitate the access of rapid mechanical reperfusion in experienced centres with a high volume of primary PCI has been associated with increased rates of reperfusion¹³², increased rates of pre-hospital diagnosis and triage¹³³, reduction in time delays¹³⁴ and reduced mortality¹³⁵. Since 1 January 2005 all patients with suspected acute coronary occlusion in the catchment area of the STEMI network in the region of Östergötland, Sweden, are considered for primary PCI. In the early years, before the results of the HORIZON-AMI¹⁰⁹ and FINESSE¹⁰⁷ studies were available, a majority of patients were treated with pre-hospital abciximab. We demonstrated in paper I that this strategy was feasible in consecutive STEMI patients admitted to our cath-lab and was associated with a high rate of patency of the IRA. Also in paper III and IV a high frequency of pre-treatment with abciximab seemed to be related to a high grade of TIMI 2-3 in the IRA. In comparison with abciximab given at the cath-lab after a diagnostic angiography, the pre-hospital administration was not associated with an excess in bleeding rates. There were no differences between the early (pre-hospital) and late group regarding mortality. However, this was a small study, unlikely to reveal statistical differences in death or MACE.

THE BENEFITS OF A PATENT IRA

Pre-procedural normal flow has been shown to be an independent determinant of survival in patients with STEMI treated with primary PCI²⁶, especially in high risk patients¹³⁶. Since the dawn of reperfusion for STEMI, studies have shown a benefit from early reperfusion of occluded arteries to reduce left ventricular function and improve survival. The capability of pharmacological treatment to establish antegrade flow in the IRA has been documented in numerous trials and with different agents. In the GUSTO 1 trial¹⁵ reperfusion with the more effective thrombolytic agent

t-pa achieved higher rates of TIMI 3 flow at 90 minutes compared to Streptokinase. After 180 minutes the rates were similar and the benefit of reduced mortality with t-pa was attributed the earlier patency of the IRA with this agent ¹³⁷. Moreover, trials with pre-hospital thrombolysis have consistently shown a survival benefit ^{138,139}. This strategy has been associated with an earlier time of reperfusion by more than two hours compared to in-hospital treatment ¹⁴⁰. In a study investigating the influence of pre-hospital administration of aspirin and heparin early treatment was associated with a patent IRA in 31 % vs. 20 % in the hospital-treated group ¹⁴¹. Antiplatelet therapy with clopidogrel given as pre-treatment is associated with a higher rate of initial patency of the IRA ¹⁴². A more pronounced effect on ischemic adverse events is seen with the higher loading dose of 600 mg vs. 300 mg ¹⁴³. Upstream treatment with clopidogrel has been associated with reduced mortality in observational studies ^{144,145}.

PRE-TREATMENT WITH GLYCOPROTEIN IIB/IIIA INHIBITORS

Several trials, most of them performed without pre-treatment with clopidogrel, have shown a higher rate of IRA patency with early administration of Gp IIb/IIIa inhibitors ^{82,85,87,89,94,146,147}. However, it has been difficult to verify a significant reduction in mortality ^{148,149}. In a study from Leiden all patients were given 600 mg clopidogrel in the cath-lab. In comparison with historical controls who received abciximab at the start of PCI, abciximab in the ambulance improved early reperfusion and was associated with smaller infarct size and lower risk of heart failure ⁹⁰. Data published from the APEX-MI trial suggest that pre-treatment with Glycoprotein inhibitors, in particular abciximab, is associated with significant reduction of mortality at three months. In that study one fourth of patients were on treatment with a thienopyridine before arriving at the cath-lab ¹⁵⁰. However, the FINESSE study did not show a benefit of pre-treatment with abciximab ¹⁰⁷ even though pre-treatment with abciximab was associated with an initial patency of the IRA in 43.7% of patients vs. 32.7% for abciximab given in the cath-lab ¹⁵¹.

In the BRAVE 3 study, patients were randomized to pre-treatment with abciximab or placebo on top of a 600 mg loading dose of clopidogrel given in average 75 minutes before PCI. The study could not demonstrate any reduction of infarct size, the primary endpoint, with early given abciximab¹⁰⁶. In the On-TIME 2 trial patients were treated with high dose tirofiban (or placebo) in the ambulance and at the same time received 600 mg clopidogrel, 500 mg ASA and 5000 U heparin. The study found significantly better resolution of ST segment elevation 60 minutes after PCI in patients pre-treated with tirofiban. Moreover, in a pooled analysis with addition of 414 patients from an open label study to the On-TIME 2 study population, there was a strong trend ($p=0.051$) for reduced mortality with tirofiban given in the ambulance⁹². However, these results could not be confirmed in a similar patient population in the multicentre AGIR-2 study which showed no difference in IRA patency or ST resolution between patients given tirofiban in the ambulance vs. at the cath-lab¹⁰⁴.

In a small randomized study abciximab given 90 minutes before primary PCI in addition to 600 mg clopidogrel was found to result in more frequent IRA patency (45.8 vs. 18.5 %) in patients in the early group vs. the cath-lab group¹⁰⁵. Finally, the EGYPT meta-analysis showed that early administration of Gp IIb/IIIa inhibitors was associated with significantly better patency of the IRA before PCI, better ST-segment resolution⁹⁶ and a benefit in mortality for abciximab¹⁵². Based on these results the recently published guidelines on STEMI from the European Society of Cardiology have given upstream treatment with Gp IIb/IIIa inhibitors a Class II B, Level B recommendation³⁷.

IMPLICATIONS OF STUDIES WITH GLYCOPROTEIN INHIBITORS

How should these studies be interpreted? Firstly there seems to be a relationship between the benefit of treatment with Glycoprotein IIb/IIIa inhibitor and the patient's risk profile⁷⁹. Analysis of the FINESSE trial indicated that patients with anterior myocardial infarction¹⁵³ and patients with

presumed occlusion < 4 h and in need of interhospital transfer¹⁰⁸ could benefit from facilitation with a reduced dose reteplase + abciximab. Secondly, it is probable that the effect of Gp IIb/IIIa inhibitor treatment is most pronounced in the early phase of coronary occlusion when the thrombus is fresh. In vitro studies have shown that abciximab can disperse formed platelet aggregates¹⁵⁴ and that this effect could be time dependent¹⁵⁵. Thrombus extracted during primary PCI has shown white, friable thrombus 90 minutes after symptom onset while thrombus extracted after 6.5 hours appeared red and compact. Scanning electron microscopy of these thrombi showed a platelet rich thrombus with small amounts of fibrin in the former case and highly, organized fibrin rich thrombus with erythrocytes in the latter¹⁵⁶. In the BRAVE 3 trial with no effect on infarct size of abciximab given at an early stage in addition to clopidogrel the median ischemic time was 4.5 hours¹⁰⁶. This time interval may be too long for adjunctive therapy with Gp IIb/IIIa inhibitors to be able to provide additive benefits regarding infarct size. In the trial, as for the HORIZON-AMI trial¹⁰⁹ a relatively low-risk population was involved. The intricate balance of weighing bleeding risk against effective anti-ischemic therapy could have privileged complications of bleeding in these trials.

THE FUTURE OF FACILITATED PCI

Future research is needed to elucidate the best pre-hospital pharmacological strategy in patients with STEMI, especially in patients with high risk and short duration of symptoms. The role of thrombolysis in this setting is under investigation¹⁵⁷. How new platelet inhibitors should be used in the pre-treatment of patients with STEMI needs to be clarified¹⁵⁸⁻¹⁶¹. Moreover, the role of pre-hospital administration of bivalirudin is not clear¹⁶², and it is not yet clear if it is superior to pre-treatment with Glycoprotein IIb/IIIa inhibitors¹⁶³. The INFUSE-AMI trial showed a reduction of infarct size in patients who were treated with abciximab in addition to bivalirudin¹⁶⁴. However, this result may have been due to the very local delivery of the drug by a microporous “weeping”

catheter (ClearWay RX Local Therapeutic Infusion Catheter) ¹⁶⁵. Other studies have shown no difference between intracoronary and intravenous administration of abciximab ¹⁶⁶.

In conclusion, it seems that the benefit of pre-treatment with glycoprotein inhibitors is most pronounced early in the evolution of acute coronary occlusion and in this stage the risk-benefit ratio may be in favour of the treatment in patients with a high ischemic risk and at the same time a low bleeding risk. Risk scores to evaluate these risks are available and clinically easy to use ^{167,168}. Furthermore, bleeding risk can be reduced by using the radial artery for vascular access in primary PCI ^{169,170}.

STRAIN ANALYSIS ON CINE MRI (PAPER II)

In paper II we showed that new feature-tracking software applied on cine MRI images could differentiate scarred segments in anterior myocardial infarction from corresponding non-scar segments. The intra- and interobserver variability was low. Most of the information was derived from radial strain. A cut-off value 38.8 % could identify segments with > 50% scar area within the LAD distribution with 80% sensitivity and 86% specificity. The radial measures correlated well with left ventricular function indicating that important and relevant functional information can be collected and used in evaluating treatment effects in patients with STEMI. The functional measures could reflect the impact of scarring on left ventricular function.

Left ventricular ejection fraction ^{171,172} and infarct size ¹⁷³ measured with ceMRI are established prognostic factors after STEMI. Whether this also holds true for the studied functional measures requires further investigation. Moreover, the study was done on isolated anterior

infarction. Larger studies need to be performed to investigate if the results apply to patients with more extensive coronary disease and infarctions with subendocardial distribution. In view of declining mortality in patients with STEMI treated with primary PCI larger cohorts are needed to demonstrate survival benefits of new treatments/strategies. In a situation of limited resources the demonstration of the effect of a given therapy may be important in guiding the selection of proper therapy in future studies. The feature-tracking software could become a tool to investigate effects of a given therapy on regional and global myocardial function. The value of its potential for giving information on the motion of infarcted segments is being investigated in on-going studies. Finally, it might be possible to avoid the use of gadolinium contrast thereby reducing patient time in the MR scanner, reducing costs and also allowing the use of cardiac MRI in patients with renal insufficiency.

THE IMPACT OF HEALTH CARE DELAY ON INFARCT SIZE (PAPER III)

We demonstrated in paper III a relationship between time from FMC to a patent artery and infarct size. The relationship was weak ($r=0.27$) and in multivariable analysis other factors such as LAD as the IRA, active smoking and an occluded artery at the first angiogram seemed to have greater influence on infarct size than time per se. There are several possible explanations for the weak relationship between health care delay and infarct size. Firstly, 37% of patients had a patent IRA at the first angiogram. Most probably the IRA was patent before insertion of the diagnostic catheter and the exact time of patency is not possible to decide in our study, and as a result, this may dilute the relationship between time delay and scar size. The median symptom onset to PCI was in excess of 3 hours. As indicated by clinical studies^{174,175} the effect of primary PCI on reduction of infarct size is greatest during the first 2 hours of coronary occlusion. Finally, the relative infarct size in our study was only 7% which reduces the possibility of demonstrating a significant relationship based on time delay to opening of the IRA.

Many studies have shown a relationship between mortality and various delay times^{34,35,40,42,44,45,47,48,176-180}. The main problem with the interpretation of these studies is that the relationship between delay time to treatment with PCI and outcome is evaluated from observational data. For obvious reason it is not ethical to perform a randomised study where one group of patients in the study would be randomized so that intervention with primary PCI was postponed for the group. In fact, the only data we have on randomized delay in reperfusion have been obtained from studies that compare pre-hospital with in-hospital thrombolysis. It is not possible to do such a study in primary PCI. One could compare patients admitted to a spoke hospital and in need of interhospital transfer with patients admitted directly to the hospital performing PCI. However, this would not include patients admitted directly to the cath-lab by the EMS, patients who are the majority of patients at least in our STEMI network.

As shown in the study by Löwel, who reported a mortality of 30% during the first hour of myocardial infarction¹⁸¹, and indicated in the study by Aquaro¹⁸², early presenters have a high risk of dying whereas late presenters probably are “survivors”. This is true by analogy with the high risk of dying in the early phase of dissection of the ascending aorta¹⁸³.

Recently Gersh and Stone presented a hypothetical relationship between duration of ischemia before reperfusion and mortality, Figure 15¹⁸⁴. According to this hypothesis there would be no significant benefit of reducing total ischemic time from 12 to 6 hours, and the effect of reducing total delay time from 6 to 3 hours would also have only a modest effect on mortality. Another hypothetical association proposed by Terkelsen et.al is shown in Figure 16³³. This hypothesis states that early presenters have the highest risk but also the greatest benefit of early perfusion with an outcome comparable to patients presenting late. The limited importance of reducing treatment delay in patient presenting late as proposed by Gersh (Figure 15) overlooks the confounding role of patient delay according to Terkelsen. It is probably not correct to estimate the beneficial effects of reduction

of time delays for individuals based on observational data. Therefore the often cited statement by de Luca that every 30 minute increase in time delay increases mortality by 7.5% ⁴⁴ may be an underestimation of the true effect of improving delay times. From a pragmatic viewpoint and from the patient's perspective every effort should be done to keep time delays to a minimum. This view is also in keeping with the spirit of the recently published guidelines from the ESC ³⁷.

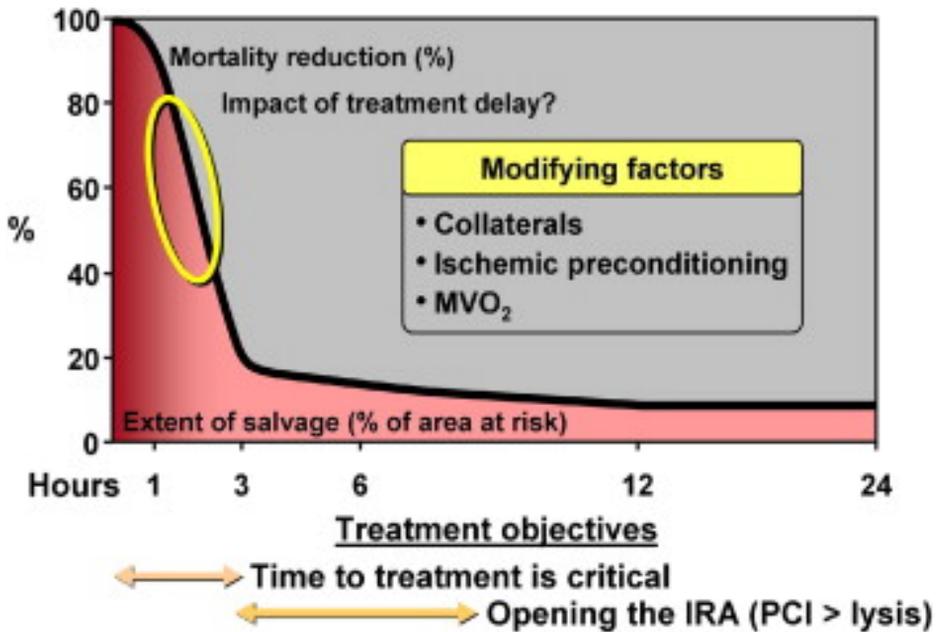


Figure 15. Relationship between duration of ischemia and mortality. Reprinted with permission from Elsevier.

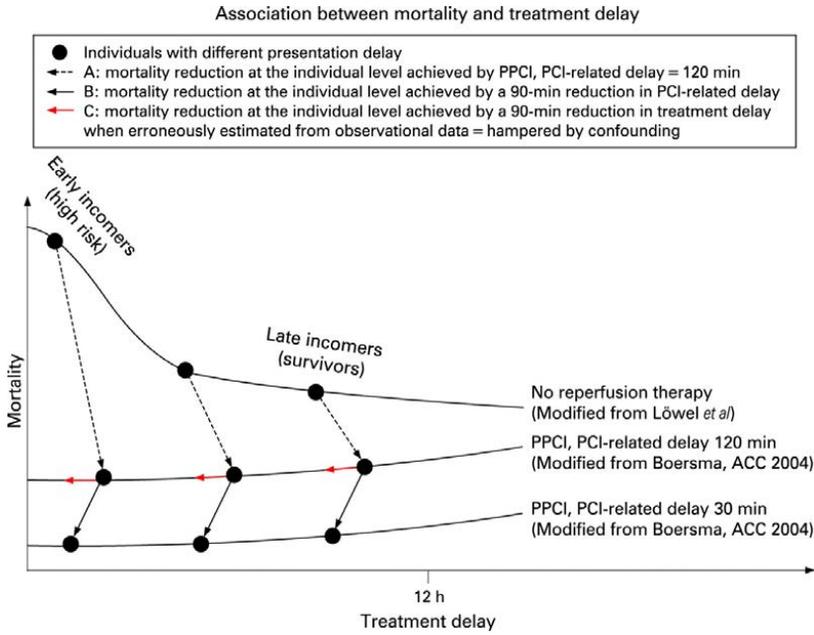


Figure 161. Hypothetical association between treatment delay and mortality in patients with ST elevation myocardial infarction. Dashed arrows represent the beneficial effect achieved by primary PCI at a PCI related delay of 120 min. B, solid black arrows represent the additional beneficial effect achieved by primary PCI at the individual level when reducing PCI-related delay from 120 to 30 min. C, red arrows indicate confounding when a beneficial effect of reducing time to treatment at the individual level is estimated from aggregated data. From *Terkelsen et al. Reprinted with permission from BMJ publishing group.*

CAN HEALTH CARE DELAY TIME BE IMPROVED (PAPER IV)?

Our STEMI network is characterized by a high frequency of field triage and direct admission from ambulance to the cath-lab. Interestingly, the percentage of patients admitted directly from ambulance in our network was 46% in the STEMI 2005 study (Paper I), and this increased to 66% among patients studied during late 2010 (Paper IV). This could be an effect of implementation of the STEMI network itself ¹³³. We identified areas of time delays and through reorganisation of logistics and continuous feedback on time delays we were able to reduce time from FMC to a patent artery with six minutes and time from diagnosis to arrival at the cath-lab with 12 minutes. For patients admitted by ambulance we chose to define FMC as the time when the patient called the EMS. The updated ESC guidelines have defined this time as the time when the patient is assessed by the EMS in the field ³⁷. The time between the time at which the patient called the EMS to the time of arrival of the ambulance at the scene was eight minutes (6-15 IQR) in our study. If we use the definition as proposed by the ESC guidelines, the time from FMC to a patent artery was reduced from 106 to 96 minutes and a significant reduction from FMC to arrival at the cath lab from 78 to 66 minutes, $p=0.04$.

CAN WE ACHIEVE THE TIME GOALS SET BY THE ESC?

The ESC recommends that FMC to primary PCI (in the guidelines the time when the IRA is wired) be no more than 90 minutes. In early presenters with a large area at risk the time frame is even narrower, < 60 minutes. In our network the median time from FMC (ESC definition) to balloon/thrombectomy was 100 minutes in the postintervention group. That is 10 minutes longer than the time proposed by the ESC. Please note that this is the median time and that a substantial proportion of patients were treated outside the time goal of the ESC. In patients admitted from the ambulance directly to the cath-lab FMC (ESC definition) to a patent artery was 91 minutes, still above the time goal.

Our delay times are almost identical to time delays reported by Terkelsen et.al for patients admitted directly by the EMS to the cath-lab¹⁸⁵. The transport time in our study though was 20 minutes longer, which was also reflected in a 20 minute longer time from FMC to balloon inflation in our patients. Randomized studies have reported similar time delays for symptom to balloon^{92,100,103,164,176,185-188} and it seems that our time delays are in line with top performing hospitals in Sweden³⁰.

The main part of reduction in health care time in our study was attributed to shortening of the time to decision by the cardiologist on call. The probable cause of this reduction was the central evaluation of ECG and the decision to have an attending cardiologist on site 24/7. Work is in progress to examine if regular training of personnel in the cath-lab in analogy with simulated advanced CPR can reduce delay times in the cath-lab.

SUMMARY

The main focus of this thesis was to examine the idea of facilitated primary PCI with glycoprotein IIb/IIIa inhibitors (abciximab) and the impact of health care delay time on infarct size and the feasibility of reducing the health care delay time. We also investigated if new feature-tracking software was able to identify the myocardial scar on cardiac MRI. We have shown that abciximab given as pre-treatment is associated with a patent artery in 46% of patients. We have demonstrated a relationship (weak) between health care delay time and infarct size and have shown that health care delay time probably can be reduced by having an attending cardiologist on site 24/7 and by making a central evaluation of ECG in patients with suspected STEMI. Finally, the capability of the new software to identify myocardial segments with scar holds promise for its use in future studies evaluating myocardial function.

FUTURE RESEARCH

The concept of facilitated primary PCI in patients presenting early and with high risk needs to be further elucidated, especially with the new platelet inhibitors that have come on the market in the past several years. Possible studies could investigate if there is a difference between infarct size and myocardial function if these agents are given at FMC instead of at the cath-lab. The question is if there will be an additional effect of glycoprotein IIb/IIIa inhibitors or bivalirudin in this setting. One could also study if the effect of glycoprotein IIb/IIIa inhibitor therapy is greater if given very locally by a special balloon delivery device than if it is given intravenously in a pre-hospital setting. Moreover, it is possible that the radial route for vascular access could tip the risk – benefit ratio between bivalirudin and glycoprotein inhibitors in favour of the latter. Given the potential effect of new oral platelet inhibitors it is possible that bivalirudin is no better than Heparin or Enoxaparin in reducing ischemic events and keeping bleeding complications at a low level in patients with STEMI.

Finally, another interesting line to investigate is if pre-hospital cooling with cold saline and use of an intravascular cooling device at the cath-lab can reduce infarct size^{189,190}.



CONCLUSION

- When abciximab was given early as pre-treatment to consecutive patients with STEMI and planned primary PCI a patent IRA at the first angiogram was obtained in 46% of cases. This was accomplished without increase in bleeding rates in comparison to abciximab given at the cath-lab.
- A weak relationship was found between time from FMC to a patent artery and infarct size measured with ceMRI. In multivariate analysis factors like an occluded artery on the diagnostic angiogram, anterior infarction and smoking seemed to have a greater influence on infarct size than time per se.
- Specific areas of time delays were identified in our STEMI network resulting in our making the following modifications in our protocol: prioritize ECG recording by EMS personnel at the scene, evaluate ECG on patients with suspected STEMI centrally and start the PCI procedure when two out of three PCI team members are on site.
- We could reduce time from FMC to a patent artery by six minutes and time from diagnosis of STEMI to arrival at the cath-lab by 11 minutes. In patients admitted directly to the cath-lab from the EMS the time from FMC to a patent artery was 91 minutes, which is in line with the recommendations of the heart societies in Europe and US.
- Feature tracking analysis of cine MR images was shown to be able to detect myocardial scar in anterior infarction with good sensitivity and specificity without the need to give gadolinium contrast.



POPULÄRVETENSKAPLIG SAMMANFATTNING (SUMMARY IN SWEDISH)

Hjärtinfarkt orsakas i de flesta fall av en bristning av ett förkalkat plack i något av hjärtats kranskärl. På så sätt kommer blodet i kontakt med innehåll i själva kärlväggen vilket uppfattas som ett inre sår som kroppen vill läka. Under dessa omständigheter kan det bildas en trombos ("blodpropp") inne i kranskärl som leder till att de celler i hjärtmuskeln som försörjs av kärlet inte får sin nödvändiga blodförsörjning och med tiden dör. Att återställa och säkra blodflödet snabbt och effektivt är målet med modern hjärtinfarkt behandling och uppbyggandet av hjärtinfarktcentra med möjlighet till akut ballongvidgning har skett i Sverige och de flesta länder i västvärlden.

Ett av syftena med avhandlingen var att studera effekten av läkemedlet abciximab (minskar blodplättarnas förmåga att klumpa ihop sig) givet som förbehandling till patienter med hjärtinfarkt och där man planerade akut ballongvidgning (**Delarbete I**). Det visade sig att de patienter som fick läkemedlet på väg till infarktcentret hade ett öppet kärl i nästan hälften av fallen jämfört med de som inte hade fått sådan förbehandling. Någon skillnad i frekvensen av allvarliga blödningar, ny hjärtinfarkt eller död upp till ett år efter hjärtinfarkten kunde inte ses.

Undersökning med magnetkamera är sannolikt den bästa metoden idag för att se och kvantifiera storleken på en hjärtinfarkt. I **delarbete II** undersöktes patienter med magnetkamera sex veckor efter att de drabbats av akut hjärninfarkt och behandlats med akut ballongvidgning. Syftet var att utreda om en ny mjukvara kunde identifiera områden i hjärtat som drabbats av en stor skada i samband med infarkten utan att använda speciell kontrast som normalt används vid denna typ av undersökning. För att kunna se infarkten med magnetröntgen så behöver man ge s.k. gadolinium kontrast som gör att infarkten lyser vit på magnetröntgen bilderna. Kontrasten innebär en viss kostnadsökning och tidsförlängning av proceduren och kan vara skadlig för patienter med nedsatt njurfunktion. Studien visade att den nya mjukvaran kunde identifiera 80% av skadade områden med 86% säkerhet utan att behöva ovan nämnda kontrast.

I den tredje studien (**delarbete III**) undersökte vi relationen mellan tiden från att patienten tar kontakt med sjukvården tills det att man kan konstatera ett normalt blodflöde i det drabbade kranskärl och hjärtinfarktens storlek. Vi undersökte 89 patienter som drabbats av hjärtinfarkt och behandlats med akut ballongvidgning. Dessa fick genomgå undersökning med magnetkamera drygt

en månad efter infarkten och infarktens storlek mättes. Vi kunde konstatera ett samband mellan den tid som sjukvården behövde för att få patienten till hjärtinfarktcentrat och öppna upp kranskärl och hjärtinfarktens storlek. Även andra faktorer som vilket kärl som var drabbat, om patienten var rökare och om kärlet var helt tilltäppt vid ingreppets början hade betydelse för skadans storlek.

Att ta hand om en patient med hjärtinfarkt, från det att patienten ringer 112 till att ambulansen är på plats, EKG har analyserats av hjärtläkare, beslut har tagits om akut ballongvidgning och patienten transporterats och omhändertagits på ett infarktcenter är en komplicerad process, speciellt under jourtid, d.v.s. helger och nätter. I det sista arbetet (**delarbete IV**) gjorde vi en detaljerad analys på hur mycket tid varje del i denna process tar. Efter diskussion med personer engagerade i denna process (ledande personer på lokala sjukhus, ambulansvården och hjärtinfarktcentret) beslöt vi att förändra tre nyckelprocesser i denna kedja; 1. Ambulansen prioriterar att ta och sända elektroniskt EKG, 2. Alla EKG på misstänkt hjärtinfarkt analyseras på hjärtinfarkt centret och 3. Ballongvidgning påbörjas redan när två av tre medlemmar i "Ballong teamet" är på plats på infarktcentret. Samtidigt infördes oberoende av studien en hjärtjour på hjärtinfarktcentret 24 timmar om dygnet 7 dagar i veckan. Tidsåtgången på 69 infarkt patienter analyserades före ovanstående förändringar. Efter att förändringarna genomförts analyserades tidsåtgången på en motsvarande grupp på 89 patienter. Vi fann att tiden från den första kontakten med sjukvården till ett öppet kärl minskade med sex minuter och tiden från diagnos av hjärtinfarkt till ankomst på infarkt centret minskade med 11 minuter efter ovanstående förändringar. Den största anledningen till denna förbättring verkade vara en snabbare beslutsprocess efter det att ett EKG som visade tecken på hjärtinfarkt skickats till infarkt centret.

Sammanfattning

Förbehandling med blodproppsförebyggande läkemedel abciximab bidrog till ett öppet infarktkärl innan behandling med ballong vidgning hos nästan hälften av patienterna. Vidare fann vi att ett snabbare omhändertagande av patienter med hjärtinfarkt var relaterat till mindre infarktstorlek mätt med magnetkamera. Detta omhändertagande kunde förbättras ytterligare med riktade förändringar av organisationen som tog hand om och behandlade patienter med hjärtinfarkt. Slutligen så kunde en ny mjukvara som användes på rörliga bilder tagna med magnetkamera upptäcka stora infarkter med rimlig känslighet och säkerhet utan att behöva speciell röntgen kontrast som normalt behövs för att upptäcka infarktskador med magnetkamera.

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REFERENCES

1. Jernberg T, Held C, Johansson P. Årsrapport SWEDEHEART 2010. www.ucr.uu.se/swedeheart/index.php/arsrapporter.
2. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, et al. Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. *Lancet*. Feb 26 2000;355(9205):688-700.
3. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. Jun 10 2010;362(23):2155-2165.
4. Roger VL, Go AS, Lloyd-Jones DM, et al. Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation*. Jan 3 2012;125(1):188-197.
5. Benson R. The present status of coronary arterial disease. *Arch Pathol Lab Med*. 1926;2:876-916.
6. Falk E. Plaque rupture with severe pre-existing stenosis precipitating coronary thrombosis. Characteristics of coronary atherosclerotic plaques underlying fatal occlusive thrombi. *British heart journal*. Aug 1983;50(2):127-134.
7. Maseri A, Chierchia S, Davies G. Pathophysiology of coronary occlusion in acute infarction. *Circulation*. Feb 1986;73(2):233-239.
8. Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. *Laboratory investigation; a journal of technical methods and pathology*. Jun 1979;40(6):633-644.
9. Hedstrom E, Engblom H, Frogner F, et al. Infarct evolution in man studied in patients with first-time coronary occlusion in comparison to different species - implications for assessment of myocardial salvage. *J Cardiovasc Magn Reson*. 2009;11:38.
10. Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. *Circulation*. Jul 1992;86(1):81-90.
11. Kloner RA, Shook T, Antman EM, et al. Prospective temporal analysis of the onset of preinfarction angina versus outcome: an ancillary study in TIMI-9B. *Circulation*. Mar 24 1998;97(11):1042-1045.
12. Risk stratification and survival after myocardial infarction. *N Engl J Med*. Aug 11 1983;309(6):331-336.
13. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). *Lancet*. Feb 22 1986;1(8478):397-402.
14. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet*. Aug 13 1988;2(8607):349-360.
15. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med*. Sep 2 1993;329(10):673-682.
16. Simes RJ, Topol EJ, Holmes DR, Jr., et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. *Circulation*. Apr 1 1995;91(7):1923-1928.
17. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more

- than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. *Lancet*. Feb 5 1994;343(8893):311-322.
18. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet*. Sep 21 1996;348(9030):771-775.
 19. Morrow DA, Antman EM, Sayah A, et al. Evaluation of the time saved by prehospital initiation of reteplase for ST-elevation myocardial infarction: results of The Early Retavase-Thrombolysis in Myocardial Infarction (ER-TIMI) 19 trial. *J Am Coll Cardiol*. Jul 3 2002;40(1):71-77.
 20. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *JAMA*. May 24-31 2000;283(20):2686-2692.
 21. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. EMERAS (Estudio Multicentrico Estreptoquinasa Republicas de America del Sur) Collaborative Group. *Lancet*. Sep 25 1993;342(8874):767-772.
 22. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation*. Jul 1987;76(1):142-154.
 23. Short R. In search of Andreas Roland Gruntzig, MD (1939-1985). *Circulation*. Aug 28 2007;116(9):f49-53.
 24. King SB, 3rd. Angioplasty from bench to bedside to bench. *Circulation*. May 1 1996;93(9):1621-1629.
 25. Meyer J, Merx W, Dorr R, Lambertz H, Bethge C, Effert S. Successful treatment of acute myocardial infarction shock by combined percutaneous transluminal coronary recanalization (PTCR) and percutaneous transluminal coronary angioplasty (PTCA). *Am Heart J*. Jan 1982;103(1):132-134.
 26. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med*. Mar 11 1993;328(10):673-679.
 27. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med*. Mar 11 1993;328(10):680-684.
 28. Lange RA, Hillis LD. Immediate angioplasty for acute myocardial infarction. *N Engl J Med*. Mar 11 1993;328(10):726-728.
 29. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet*. Jan 4 2003;361(9351):13-20.
 30. Jernberg T, Held C, Johansson P. Årsrapport SWEDEHEART 2011
www.ucr.uu.se/swedeheart/index.php/arsrapporter.
 31. Knot J, Widimsky P, Wijns W, et al. How to set up an effective national primary angioplasty network: lessons learned from five European countries. *EuroIntervention*. Aug 2009;5(3):299, 301-309.
 32. Nallamothu BK, Bates ER. Percutaneous coronary intervention versus fibrinolytic therapy in acute myocardial infarction: is timing (almost) everything? *Am J Cardiol*. Oct 1 2003;92(7):824-826.
 33. Terkelsen CJ, Christiansen EH, Sorensen JT, et al. Primary PCI as the preferred reperfusion therapy in STEMI: it is a matter of time. *Heart*. Mar 2009;95(5):362-369.
 34. Boersma E, Primary Coronary Angioplasty vs. Thrombolysis G. Does time matter? A pooled analysis of randomized clinical trials comparing primary percutaneous coronary intervention and in-hospital fibrinolysis in acute myocardial infarction patients. *Eur Heart J*. Apr 2006;27(7):779-788.

35. Steg PG, Bonnefoy E, Chabaud S, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation*. Dec 9 2003;108(23):2851-2856.
36. Widimsky P, Budesinsky T, Vorac D, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial--PRAGUE-2. *Eur Heart J*. Jan 2003;24(1):94-104.
37. Authors/Task Force M, Steg PG, James SK, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *Eur Heart J*. Aug 24 2012.
38. Zijlstra F, Patel A, Jones M, et al. Clinical characteristics and outcome of patients with early (<2 h), intermediate (2-4 h) and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. *Eur Heart J*. Apr 2002;23(7):550-557.
39. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. Jun 14 2000;283(22):2941-2947.
40. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol*. Nov 1998;32(5):1312-1319.
41. Brodie BR, Stuckey TD, Muncy DB, et al. Importance of time-to-reperfusion in patients with acute myocardial infarction with and without cardiogenic shock treated with primary percutaneous coronary intervention. *Am Heart J*. Apr 2003;145(4):708-715.
42. Antonucci D, Valenti R, Migliorini A, et al. Relation of time to treatment and mortality in patients with acute myocardial infarction undergoing primary coronary angioplasty. *Am J Cardiol*. Jun 1 2002;89(11):1248-1252.
43. Brodie BR, Stone GW, Cox DA, et al. Impact of treatment delays on outcomes of primary percutaneous coronary intervention for acute myocardial infarction: analysis from the CADILLAC trial. *Am Heart J*. Jun 2006;151(6):1231-1238.
44. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation*. Mar 16 2004;109(10):1223-1225.
45. De Luca G, Suryapranata H, Zijlstra F, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol*. Sep 17 2003;42(6):991-997.
46. Berger PB, Ellis SG, Holmes DR, Jr., et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation*. Jul 6 1999;100(1):14-20.
47. Brodie BR, Hansen C, Stuckey TD, et al. Door-to-balloon time with primary percutaneous coronary intervention for acute myocardial infarction impacts late cardiac mortality in high-risk patients and patients presenting early after the onset of symptoms. *J Am Coll Cardiol*. Jan 17 2006;47(2):289-295.
48. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. Jun 6 2006;47(11):2180-2186.
49. Le May MR, So DY, Dionne R, et al. A citywide protocol for primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. Jan 17 2008;358(3):231-240.
50. Borden WB, Fennessy MM, O'Connor AM, et al. Quality improvement in the door-to-balloon times for ST-elevation myocardial infarction patients presenting without chest pain. *Catheter Cardiovasc Interv*. May 1 2012;79(6):851-858.
51. Krumholz HM, Herrin J, Miller LE, et al. Improvements in door-to-balloon time in the United States, 2005 to 2010. *Circulation*. Aug 30 2011;124(9):1038-1045.

52. Krumholz HM, Bradley EH, Nallamothu BK, et al. A campaign to improve the timeliness of primary percutaneous coronary intervention: Door-to-Balloon: An Alliance for Quality. *JACC. Cardiovascular interventions*. Feb 2008;1(1):97-104.
53. Jacobs AK, Antman EM, Ellrodt G, et al. Recommendation to develop strategies to increase the number of ST-segment-elevation myocardial infarction patients with timely access to primary percutaneous coronary intervention. *Circulation*. May 2 2006;113(17):2152-2163.
54. Jollis JG, Granger CB, Henry TD, et al. Systems of Care for ST-Segment-Elevation Myocardial Infarction: A Report From the American Heart Association's Mission: Lifeline. *Circulation. Cardiovascular quality and outcomes*. Jul 1 2012;5(4):423-428.
55. Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. *N Engl J Med*. Nov 30 2006;355(22):2308-2320.
56. Bradley EH, Curry LA, Webster TR, et al. Achieving rapid door-to-balloon times: how top hospitals improve complex clinical systems. *Circulation*. Feb 28 2006;113(8):1079-1085.
57. Bradley EH, Roumanis SA, Radford MJ, et al. Achieving door-to-balloon times that meet quality guidelines: how do successful hospitals do it? *J Am Coll Cardiol*. Oct 4 2005;46(7):1236-1241.
58. Havel C, Schreiber W, Christ G, Winkler S, Herkner H. Accelerated management of patients with ST-segment elevation myocardial infarction in the ED. *The American journal of emergency medicine*. Jul 2011;29(6):650-655.
59. Kelly EW, Kelly JD, Hiestand B, Wells-Kiser K, Starling S, Hoekstra JW. Six Sigma process utilization in reducing door-to-balloon time at a single academic tertiary care center. *Progress in cardiovascular diseases*. Nov-Dec 2010;53(3):219-226.
60. Afolabi BA, Novaro GM, Pinski SL, Fromkin KR, Bush HS. Use of the prehospital ECG improves door-to-balloon times in ST segment elevation myocardial infarction irrespective of time of day or day of week. *Emergency medicine journal : EMJ*. Aug 2007;24(8):588-591.
61. Huang RL, Donelli A, Byrd J, et al. Using quality improvement methods to improve door-to-balloon time at an academic medical center. *J Invasive Cardiol*. Feb 2008;20(2):46-52.
62. Lai CL, Fan CM, Liao PC, et al. Impact of an audit program and other factors on door-to-balloon times in acute ST-elevation myocardial infarction patients destined for primary coronary intervention. *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*. Apr 2009;16(4):333-342.
63. van de Loo A, Saurbier B, Kalbhenn J, Koberne F, Zehender M. Primary percutaneous coronary intervention in acute myocardial infarction: direct transportation to catheterization laboratory by emergency teams reduces door-to-balloon time. *Clinical cardiology*. Mar 2006;29(3):112-116.
64. Kunadian B, Morley R, Roberts AP, et al. Impact of implementation of evidence-based strategies to reduce door-to-balloon time in patients presenting with STEMI: continuous data analysis and feedback using a statistical process control plot. *Heart*. Oct 2010;96(19):1557-1563.
65. Munoz D, Roettig ML, Monk L, Al-Khalidi H, Jollis JG, Granger CB. Transport Time and Care Processes for Patients Transferred With ST-Segment-Elevation Myocardial Infarction: The Reperfusion in Acute Myocardial Infarction in Carolina Emergency Rooms Experience. *Circulation. Cardiovascular interventions*. Aug 1 2012;5(4):555-562.
66. Chakrabarti A, Krumholz HM, Wang Y, Rumsfeld JS, Nallamothu BK, National Cardiovascular Data R. Time-to-reperfusion in patients undergoing interhospital transfer for primary percutaneous coronary intervention in the U.S: an analysis of 2005 and 2006 data from the National Cardiovascular Data Registry. *J Am Coll Cardiol*. Jun 24 2008;51(25):2442-2443.
67. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST-elevation myocardial infarction: quantitative review of randomised trials. *Lancet*. Feb 18 2006;367(9510):579-588.
68. Kreutzer M, Magnuson A, Lagerqvist B, Frobert O. Patent coronary artery and myocardial infarction in the era of primary angioplasty: assessment of an old problem in a new setting with data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *EuroIntervention*. Nov 2010;6(5):590-595.

69. Konstantopoulos K, Kamat SG, Schafer AI, et al. Shear-induced platelet aggregation is inhibited by in vivo infusion of an anti-glycoprotein IIb/IIIa antibody fragment, c7E3 Fab, in patients undergoing coronary angioplasty. *Circulation*. Mar 1 1995;91(5):1427-1431.
70. Kleiman NS, Raizner AE, Jordan R, et al. Differential inhibition of platelet aggregation induced by adenosine diphosphate or a thrombin receptor-activating peptide in patients treated with bolus chimeric 7E3 Fab: implications for inhibition of the internal pool of GPIIb/IIIa receptors. *J Am Coll Cardiol*. Dec 1995;26(7):1665-1671.
71. Wu D, Meiring M, Kotze HF, Deckmyn H, Cauwenberghs N. Inhibition of platelet glycoprotein IIb, glycoprotein IIb/IIIa, or both by monoclonal antibodies prevents arterial thrombosis in baboons. *Arteriosclerosis, thrombosis, and vascular biology*. Feb 1 2002;22(2):323-328.
72. Goto S, Tamura N, Ishida H. Ability of anti-glycoprotein IIb/IIIa agents to dissolve platelet thrombi formed on a collagen surface under blood flow conditions. *J Am Coll Cardiol*. Jul 21 2004;44(2):316-323.
73. Gold HK, Garabedian HD, Dinsmore RE, et al. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without exogenous plasminogen activators. Observations in animals and humans. *Circulation*. Apr 1 1997;95(7):1755-1759.
74. Antoniucci D, Rodriguez A, Hempel A, et al. A randomized trial comparing primary infarct artery stenting with or without abciximab in acute myocardial infarction. *J Am Coll Cardiol*. Dec 3 2003;42(11):1879-1885.
75. Antoniucci D, Migliorini A, Parodi G, et al. Abciximab-supported infarct artery stent implantation for acute myocardial infarction and long-term survival: a prospective, multicenter, randomized trial comparing infarct artery stenting plus abciximab with stenting alone. *Circulation*. Apr 13 2004;109(14):1704-1706.
76. Montalescot G, Antoniucci D, Kastrati A, et al. Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients' data with long-term follow-up. *Eur Heart J*. Feb 2007;28(4):443-449.
77. De Luca G, Suryapranata H, Stone GW, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. *JAMA*. Apr 13 2005;293(14):1759-1765.
78. De Luca G, Suryapranata H, Stone GW, et al. Relationship between patient's risk profile and benefits in mortality from adjunctive abciximab to mechanical revascularization for ST-segment elevation myocardial infarction: a meta-regression analysis of randomized trials. *J Am Coll Cardiol*. Feb 7 2006;47(3):685-686.
79. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. *Eur Heart J*. Nov 2009;30(22):2705-2713.
80. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*. Jun 21 2001;344(25):1895-1903.
81. Topol EJ, Neumann FJ, Montalescot G. A preferred reperfusion strategy for acute myocardial infarction. *J Am Coll Cardiol*. Dec 3 2003;42(11):1886-1889.
82. Gyongyosi M, Domanovits H, Benzer W, et al. Use of abciximab prior to primary angioplasty in STEMI results in early recanalization of the infarct-related artery and improved myocardial tissue reperfusion - results of the Austrian multi-centre randomized ReoPro-BRIDGING Study. *Eur Heart J*. Dec 2004;25(23):2125-2133.
83. van den Merkhof LF, Zijlstra F, Olsson H, et al. Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty. Results of the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot study. *J Am Coll Cardiol*. May 1999;33(6):1528-1532.
84. Ohlmann P, Reydel P, Jacquemin L, et al. Prehospital abciximab in ST-segment elevation myocardial infarction: results of the randomized, double-blind MISTRAL study. *Circulation. Cardiovascular interventions*. Feb 1 2012;5(1):69-76, S61.

85. Gibson CM, Kirtane AJ, Murphy SA, et al. Early initiation of eptifibatid in the emergency department before primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: results of the Time to Integrilin Therapy in Acute Myocardial Infarction (TITAN)-TIMI 34 trial. *Am Heart J.* Oct 2006;152(4):668-675.
86. Gabriel HM, Oliveira JA, da Silva PC, da Costa JM, da Cunha JA. Early administration of abciximab bolus in the emergency department improves angiographic outcome after primary PCI as assessed by TIMI frame count: results of the early ReoPro administration in myocardial infarction (ERAMI) trial. *Catheter Cardiovasc Interv.* Aug 2006;68(2):218-224.
87. Lee DP, Herity NA, Hiatt BL, et al. Adjunctive platelet glycoprotein IIb/IIIa receptor inhibition with tirofiban before primary angioplasty improves angiographic outcomes: results of the Tirofiban Given in the Emergency Room before Primary Angioplasty (TIGER-PA) pilot trial. *Circulation.* Mar 25 2003;107(11):1497-1501.
88. Rakowski T, Zalewski J, Legutko J, et al. Early abciximab administration before primary percutaneous coronary intervention improves infarct-related artery patency and left ventricular function in high-risk patients with anterior wall myocardial infarction: a randomized study. *Am Heart J.* Mar 2007;153(3):360-365.
89. Maioli M, Bellandi F, Leoncini M, Toso A, Dabizzi RP. Randomized early versus late abciximab in acute myocardial infarction treated with primary coronary intervention (RELAX-AMI Trial). *J Am Coll Cardiol.* Apr 10 2007;49(14):1517-1524.
90. Hassan AK, Liem SS, van der Kley F, et al. In-ambulance abciximab administration in STEMI patients prior to primary PCI is associated with smaller infarct size, improved LV function and lower incidence of heart failure: results from the Leiden MISSION! acute myocardial infarction treatment optimization program. *Catheter Cardiovasc Interv.* Aug 1 2009;74(2):335-343.
91. Cutlip DE, Ricciardi MJ, Ling FS, et al. Effect of tirofiban before primary angioplasty on initial coronary flow and early ST-segment resolution in patients with acute myocardial infarction. *Am J Cardiol.* Oct 15 2003;92(8):977-980.
92. Van't Hof AW, Ten Berg J, Heestermaans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet.* Aug 16 2008;372(9638):537-546.
93. Emre A, Ucer E, Yesilcimen K, et al. Impact of early tirofiban administration on myocardial salvage in patients with acute myocardial infarction undergoing infarct-related artery stenting. *Cardiology.* 2006;106(4):264-269.
94. Bellandi F, Maioli M, Leoncini M, Toso A, Dabizzi RP. Early abciximab administration in acute myocardial infarction treated with primary coronary intervention. *Int J Cardiol.* Mar 22 2006;108(1):36-42.
95. Hassan AK, Jukema JW, van der Laarse A, et al. Incidence, patient characteristics and predictors of aborted myocardial infarction in patients undergoing primary PCI: prospective study comparing pre- and in-hospital abciximab pretreatment. *EuroIntervention.* Mar 2009;4(5):662-668.
96. De Luca G, Gibson CM, Bellandi F, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty (EGYPT) cooperation: an individual patient data meta-analysis. *Heart.* Dec 2008;94(12):1548-1558.
97. Dudek D, Rakowski T, El Massri N, et al. Patency of infarct related artery after pharmacological reperfusion during transfer to primary percutaneous coronary intervention influences left ventricular function and one-year clinical outcome. *Int J Cardiol.* Mar 14 2008;124(3):326-331.
98. Dudek D, Siudak Z, Janzon M, et al. European registry on patients with ST-elevation myocardial infarction transferred for mechanical reperfusion with a special focus on early administration of abciximab -- EUROTRANSFER Registry. *Am Heart J.* Dec 2008;156(6):1147-1154.

99. Dziewierz A, Mielecki W, Siudak Z, et al. Early abciximab administration before primary percutaneous coronary intervention improves clinical outcome in diabetic patients with ST-segment elevation myocardial infarction (EUROTRANSFER Registry). *Atherosclerosis*. Jul 2012;223(1):212-218.
100. Rakowski T, Siudak Z, Dziewierz A, et al. Early abciximab administration before transfer for primary percutaneous coronary interventions for ST-elevation myocardial infarction reduces 1-year mortality in patients with high-risk profile. Results from EUROTRANSFER registry. *Am Heart J*. Oct 2009;158(4):569-575.
101. van 't Hof AW, Ernst N, de Boer MJ, et al. Facilitation of primary coronary angioplasty by early start of a glycoprotein 2b/3a inhibitor: results of the ongoing tirofiban in myocardial infarction evaluation (On-TIME) trial. *Eur Heart J*. May 2004;25(10):837-846.
102. Pels K, Schroder J, Witzenbichler B, et al. Prehospital versus periprocedural abciximab in ST-elevation myocardial infarction treated by percutaneous coronary intervention. *European journal of emergency medicine : official journal of the European Society for Emergency Medicine*. Dec 2008;15(6):324-329.
103. Petronio AS, De Carlo M, Strata E, et al. Impact of early abciximab administration on infarct size in patients with ST-elevation myocardial infarction. *Int J Cardiol*. Mar 8 2012;155(2):230-235.
104. El Khoury C, Dubien PY, Mercier C, et al. Prehospital high-dose tirofiban in patients undergoing primary percutaneous intervention. The AGIR-2 study. *Archives of cardiovascular diseases*. May 2010;103(5):285-292.
105. Dudek D, Rakowski T, Bartus S, et al. Impact of early abciximab administration on myocardial reperfusion in patients with ST-segment elevation myocardial infarction pretreated with 600 mg of clopidogrel before percutaneous coronary intervention. *Journal of thrombosis and thrombolysis*. Oct 2010;30(3):347-353.
106. Mehilli J, Kastrati A, Schulz S, et al. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation*. Apr 14 2009;119(14):1933-1940.
107. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med*. May 22 2008;358(21):2205-2217.
108. Herrmann HC, Lu J, Brodie BR, et al. Benefit of facilitated percutaneous coronary intervention in high-risk ST-segment elevation myocardial infarction patients presenting to nonpercutaneous coronary intervention hospitals. *JACC. Cardiovascular interventions*. Oct 2009;2(10):917-924.
109. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. May 22 2008;358(21):2218-2230.
110. Kushner FG, Hand M, Smith SC, Jr., et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. Dec 1 2009;54(23):2205-2241.
111. Ishida M, Kato S, Sakuma H. Cardiac MRI in ischemic heart disease. *Circulation journal : official journal of the Japanese Circulation Society*. Sep 2009;73(9):1577-1588.
112. Gore TB, Rollings RC, Gore AW, 3rd. The many facets of cardiovascular magnetic resonance imaging: review of background, clinical utility, and increasing use in the community hospital. *Southern medical journal*. Jul 2009;102(7):719-724.
113. Kim RJ, Fieno DS, Parrish TB, et al. Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. *Circulation*. Nov 9 1999;100(19):1992-2002.
114. Lloyd SG, Gupta H. Assessment of myocardial viability by cardiovascular magnetic resonance. *Echocardiography*. Feb 2005;22(2):179-193.

115. Mahrholdt H, Wagner A, Holly TA, et al. Reproducibility of chronic infarct size measurement by contrast-enhanced magnetic resonance imaging. *Circulation*. Oct 29 2002;106(18):2322-2327.
116. Shan K, Constantine G, Sivananthan M, Flamm SD. Role of cardiac magnetic resonance imaging in the assessment of myocardial viability. *Circulation*. Mar 23 2004;109(11):1328-1334.
117. Kim RJ, Albert TS, Wible JH, et al. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: an international, multicenter, double-blinded, randomized trial. *Circulation*. Feb 5 2008;117(5):629-637.
118. Fieno DS, Kim RJ, Chen EL, Lomasney JW, Klocke FJ, Judd RM. Contrast-enhanced magnetic resonance imaging of myocardium at risk: distinction between reversible and irreversible injury throughout infarct healing. *J Am Coll Cardiol*. Nov 15 2000;36(6):1985-1991.
119. Wagner A, Mahrholdt H, Holly TA, et al. Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. *Lancet*. Feb 1 2003;361(9355):374-379.
120. Thiele H, Kappl MJ, Linke A, et al. Influence of time-to-treatment, TIMI-flow grades, and ST-segment resolution on infarct size and infarct transmurality as assessed by delayed enhancement magnetic resonance imaging. *Eur Heart J*. Jun 2007;28(12):1433-1439.
121. Thiele H, Kappl MJ, Conradi S, Niebauer J, Hambrecht R, Schuler G. Reproducibility of chronic and acute infarct size measurement by delayed enhancement-magnetic resonance imaging. *J Am Coll Cardiol*. Apr 18 2006;47(8):1641-1645.
122. Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. *N Engl J Med*. Nov 16 2000;343(20):1445-1453.
123. Sadeghi HM, Stone GW, Grines CL, et al. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. *Circulation*. Dec 2 2003;108(22):2769-2775.
124. Sederholm Lawesson S, Todt T, Alfredsson J, Janzon M, Stenestrand U, Swahn E. Gender difference in prevalence and prognostic impact of renal insufficiency in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart*. Feb 2011;97(4):308-314.
125. Campbell NG, Varagunam M, Sawhney V, et al. Mild chronic kidney disease is an independent predictor of long-term mortality after emergency angiography and primary percutaneous intervention in patients with ST-elevation myocardial infarction. *Heart*. Jan 2012;98(1):42-47.
126. Kuo PH, Kanal E, Abu-Alfa AK, Cowper SE. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. *Radiology*. Mar 2007;242(3):647-649.
127. Stenestrand U, Wallentin L. Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA*. Jan 24-31 2001;285(4):430-436.
128. Lagerqvist B, James SK, Stenestrand U, Lindback J, Nilsson T, Wallentin L. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med*. Mar 8 2007;356(10):1009-1019.
129. Lee J, Koh D, Ong CN. Statistical evaluation of agreement between two methods for measuring a quantitative variable. *Computers in biology and medicine*. 1989;19(1):61-70.
130. Rousson V, Gasser T, Seifert B. Assessing intrarater, interrater and test-retest reliability of continuous measurements. *Statistics in medicine*. Nov 30 2002;21(22):3431-3446.
131. Miller TD, Christian TF, Hopfenspirger MR, Hodge DO, Gersh BJ, Gibbons RJ. Infarct size after acute myocardial infarction measured by quantitative tomographic 99mTc sestamibi imaging predicts subsequent mortality. *Circulation*. Aug 1 1995;92(3):334-341.
132. Kalla K, Christ G, Karnik R, et al. Implementation of guidelines improves the standard of care: the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry). *Circulation*. May 23 2006;113(20):2398-2405.

133. Ortolani P, Marzocchi A, Marrozzini C, et al. Clinical impact of direct referral to primary percutaneous coronary intervention following pre-hospital diagnosis of ST-elevation myocardial infarction. *Eur Heart J*. Jul 2006;27(13):1550-1557.
134. Sejersten M, Sillesen M, Hansen PR, et al. Effect on treatment delay of prehospital teletransmission of 12-lead electrocardiogram to a cardiologist for immediate triage and direct referral of patients with ST-segment elevation acute myocardial infarction to primary percutaneous coronary intervention. *Am J Cardiol*. Apr 1 2008;101(7):941-946.
135. Saia F, Marrozzini C, Ortolani P, et al. Optimisation of therapeutic strategies for ST-segment elevation acute myocardial infarction: the impact of a territorial network on reperfusion therapy and mortality. *Heart*. Mar 2009;95(5):370-376.
136. De Luca G, Ernst N, Zijlstra F, et al. Preprocedural TIMI flow and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol*. Apr 21 2004;43(8):1363-1367.
137. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. *N Engl J Med*. Nov 25 1993;329(22):1615-1622.
138. Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. The European Myocardial Infarction Project Group. *N Engl J Med*. Aug 5 1993;329(6):383-389.
139. Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol*. Nov 1 1997;30(5):1181-1186.
140. Feasibility, safety, and efficacy of domiciliary thrombolysis by general practitioners: Grampian region early anistreplase trial. GREAT Group. *BMJ*. Sep 5 1992;305(6853):548-553.
141. Zijlstra F, Ernst N, de Boer MJ, et al. Influence of prehospital administration of aspirin and heparin on initial patency of the infarct-related artery in patients with acute ST elevation myocardial infarction. *J Am Coll Cardiol*. Jun 5 2002;39(11):1733-1737.
142. Vlaar PJ, Svilaas T, Damman K, et al. Impact of pretreatment with clopidogrel on initial patency and outcome in patients treated with primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review. *Circulation*. Oct 28 2008;118(18):1828-1836.
143. Dangas G, Mehran R, Guagliumi G, et al. Role of clopidogrel loading dose in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty: results from the HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trial. *J Am Coll Cardiol*. Oct 6 2009;54(15):1438-1446.
144. Dorler J, Edlinger M, Alber HF, et al. Clopidogrel pre-treatment is associated with reduced in-hospital mortality in primary percutaneous coronary intervention for acute ST-elevation myocardial infarction. *Eur Heart J*. Dec 2011;32(23):2954-2961.
145. Koul S, Smith JG, Schersten F, James S, Lagerqvist B, Erlinge D. Effect of upstream clopidogrel treatment in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Eur Heart J*. Dec 2011;32(23):2989-2997.
146. Zorman S, Zorman D, Noc M. Effects of abciximab pretreatment in patients with acute myocardial infarction undergoing primary angioplasty. *Am J Cardiol*. Sep 1 2002;90(5):533-536.
147. Zeymer U, Zahn R, Schiele R, et al. Early eptifibatid improves TIMI 3 patency before primary percutaneous coronary intervention for acute ST elevation myocardial infarction: results of the randomized integrilin in acute myocardial infarction (INTAMI) pilot trial. *Eur Heart J*. Oct 2005;26(19):1971-1977.
148. Godicke J, Flather M, Noc M, et al. Early versus periprocedural administration of abciximab for primary angioplasty: a pooled analysis of 6 studies. *Am Heart J*. Nov 2005;150(5):1015.
149. Montalescot G, Borentain M, Payot L, Collet JP, Thomas D. Early vs late administration of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention of acute ST-segment elevation myocardial infarction: a meta-analysis. *JAMA*. Jul 21 2004;292(3):362-366.

150. Huber K, Holmes DR, Jr., van 't Hof AW, et al. Use of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention: insights from the APEX-AMI trial. *Eur Heart J*. Jul 2010;31(14):1708-1716.
151. Prati F, Petronio S, Van Boven AJ, et al. Evaluation of infarct-related coronary artery patency and microcirculatory function after facilitated percutaneous primary coronary angioplasty: the FINESSE-ANGIO (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events-Angiographic) study. *JACC. Cardiovascular interventions*. Dec 2010;3(12):1284-1291.
152. De Luca, Bellandi F, Huber K, et al. Early glycoprotein IIb-IIIa inhibitors in primary angioplasty-abciximab long-term results (EGYPT-ALT) cooperation: individual patient's data meta-analysis. *Journal of thrombosis and haemostasis : JTH*. Dec 2011;9(12):2361-2370.
153. Ellis SG, Tendera M, de Belder MA, et al. 1-year survival in a randomized trial of facilitated reperfusion: results from the FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) trial. *JACC. Cardiovascular interventions*. Oct 2009;2(10):909-916.
154. Marciniak SJ, Jr., Mascelli MA, Furman MI, et al. An additional mechanism of action of abciximab: dispersal of newly formed platelet aggregates. *Thrombosis and haemostasis*. Jun 2002;87(6):1020-1025.
155. Goldsmith HL, McIntosh FA, Shahin J, Frojmovic MM. Time and force dependence of the rupture of glycoprotein IIb-IIIa-fibrinogen bonds between latex spheres. *Biophys J*. Mar 2000;78(3):1195-1206.
156. Beygui F, Collet JP, Nagaswami C, Weisel JW, Montalescot G. Images in cardiovascular medicine. Architecture of intracoronary thrombi in ST-elevation acute myocardial infarction: time makes the difference. *Circulation*. Jan 17 2006;113(2):e21-23.
157. Armstrong PW, Gershlick A, Goldstein P, et al. The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study. *Am Heart J*. Jul 2010;160(1):30-35 e31.
158. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. Feb 28 2009;373(9665):723-731.
159. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation*. Nov 23 2010;122(21):2131-2141.
160. Berger JS, Roe MT, Gibson CM, et al. Safety and feasibility of adjunctive antiplatelet therapy with intravenous elinogrel, a direct-acting and reversible P2Y12 ADP-receptor antagonist, before primary percutaneous intervention in patients with ST-elevation myocardial infarction: the Early Rapid ReversAl of platelet thromboSis with intravenous Elinogrel before PCI to optimize reperfusion in acute Myocardial Infarction (ERASE MI) pilot trial. *Am Heart J*. Dec 2009;158(6):998-1004 e1001.
161. Harrington RA, Stone GW, McNulty S, et al. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. Dec 10 2009;361(24):2318-2329.
162. Sejersten M, Nielsen SL, Engstrom T, Jorgensen E, Clemmensen P. Feasibility and safety of prehospital administration of bivalirudin in patients with ST-elevation myocardial infarction. *Am J Cardiol*. Jun 15 2009;103(12):1635-1640.
163. Hirschl MM, Mayr H, Erhart F, et al. Prehospital treatment of patients with acute myocardial infarction with bivalirudin. *The American journal of emergency medicine*. Jan 2012;30(1):12-17.
164. Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction: The INFUSE-AMI Randomized Trial. *JAMA*. Mar 25 2012.
165. Deibele AJ, Michael Gibson C. Intracoronary delivery of eptifibatide with the ClearWay(R) RX infusion catheter. *Catheter Cardiovasc Interv*. Feb 1 2011;77(2):222-227.

166. Thiele H, Wohrle J, Hambrecht R, et al. Intracoronary versus intravenous bolus abciximab during primary percutaneous coronary intervention in patients with acute ST-elevation myocardial infarction: a randomised trial. *Lancet*. Mar 10 2012;379(9819):923-931.
167. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. Oct 24 2000;102(17):2031-2037.
168. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. Jun 8 2010;55(23):2556-2566.
169. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. Apr 23 2011;377(9775):1409-1420.
170. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial Versus Femoral Randomized Investigation in ST-Segment Elevation Acute Coronary Syndrome: The RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) Study. *J Am Coll Cardiol*. Jul 27 2012.
171. Nicolosi GL, Latini R, Marino P, et al. The prognostic value of predischarge quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 Trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Eur Heart J*. Nov 1996;17(11):1646-1656.
172. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. Sep 3 1992;327(10):669-677.
173. Bruder O, Breuckmann F, Jensen C, et al. Prognostic impact of contrast-enhanced CMR early after acute ST segment elevation myocardial infarction (STEMI) in a regional STEMI network: results of the "Herzinfarktverbund Essen". *Herz*. Mar 2008;33(2):136-142.
174. Stone GW, Dixon SR, Grines CL, et al. Predictors of infarct size after primary coronary angioplasty in acute myocardial infarction from pooled analysis from four contemporary trials. *Am J Cardiol*. Nov 1 2007;100(9):1370-1375.
175. Francone M, Bucciarelli-Ducci C, Carbone I, et al. Impact of primary coronary angioplasty delay on myocardial salvage, infarct size, and microvascular damage in patients with ST-segment elevation myocardial infarction: insight from cardiovascular magnetic resonance. *J Am Coll Cardiol*. Dec 1 2009;54(23):2145-2153.
176. Terkelsen CJ, Sorensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA*. Aug 18 2010;304(7):763-771.
177. Nallamothu B, Fox KA, Kennelly BM, et al. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart*. Dec 2007;93(12):1552-1555.
178. Rathore SS, Curtis JP, Chen J, et al. Association of door-to-balloon time and mortality in patients admitted to hospital with ST elevation myocardial infarction: national cohort study. *BMJ*. 2009;338:b1807.
179. Lambert L, Brown K, Segal E, Brophy J, Rodes-Cabau J, Bogaty P. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. *JAMA*. Jun 2 2010;303(21):2148-2155.
180. Wang TY, Nallamothu BK, Krumholz HM, et al. Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. *JAMA*. Jun 22 2011;305(24):2540-2547.

181. Lowel H, Lewis M, Hormann A. [Prognostic significance of prehospital phase in acute myocardial infarct. Results of the Augsburg Myocardial Infarct Registry, 1985-1988]. *Deutsche medizinische Wochenschrift*. May 10 1991;116(19):729-733.
182. Aquaro GD, Pingitore A, Strata E, et al. Relation of pain-to-balloon time and myocardial infarct size in patients transferred for primary percutaneous coronary intervention. *Am J Cardiol*. Jul 1 2007;100(1):28-34.
183. Appelbaum A, Karp RB, Kirklin JW. Ascending vs descending aortic dissections. *Annals of surgery*. Mar 1976;183(3):296-300.
184. Gersh BJ, Stone GW. Pharmacological facilitation of coronary intervention in ST-segment elevation myocardial infarction: time is of the essence. *JACC. Cardiovascular interventions*. Dec 2010;3(12):1292-1294.
185. Terkelsen CJ, Lassen JF, Norgaard BL, et al. Reduction of treatment delay in patients with ST-elevation myocardial infarction: impact of pre-hospital diagnosis and direct referral to primary percutaneous coronary intervention. *Eur Heart J*. Apr 2005;26(8):770-777.
186. Wijnbergen I, Helmes H, Tijssen J, et al. Comparison of drug-eluting and bare-metal stents for primary percutaneous coronary intervention with or without abciximab in ST-segment elevation myocardial infarction: DEBATER: the Eindhoven reperfusion study. *JACC. Cardiovascular interventions*. Mar 2012;5(3):313-322.
187. Nielsen PH, Terkelsen CJ, Nielsen TT, et al. System delay and timing of intervention in acute myocardial infarction (from the Danish Acute Myocardial Infarction-2 [DANAMI-2] trial). *Am J Cardiol*. Sep 15 2011;108(6):776-781.
188. Marzocchi A, Manari A, Piovaccari G, et al. Randomized comparison between tirofiban and abciximab to promote complete ST-resolution in primary angioplasty: results of the facilitated angioplasty with tirofiban or abciximab (FATA) in ST-elevation myocardial infarction trial. *Eur Heart J*. Dec 2008;29(24):2972-2980.
189. Gotberg M, Olivecrona GK, Koul S, et al. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circulation. Cardiovascular interventions*. Oct 2010;3(5):400-407.
190. Gotberg M, van der Pals J, Gotberg M, et al. Optimal timing of hypothermia in relation to myocardial reperfusion. *Basic research in cardiology*. Sep 2011;106(5):697-708.