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Reperfusion therapy in acute ST-elevation myocardial infarction

a comparison between primary percutaneous intervention and thrombolysis in a short- and long-term perspective

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Dedicated to the 205 patients who, although being critically ill,
had the courage and strength to participate in the SWEDES study.

ABSTRACT

Approximately 35,000 people suffer from a heart attack in Sweden annually. Among them, approximately 8000 are diagnosed with a ST-elevation myocardial infarction (STEMI) where timely reperfusion has been shown to save lives. Previous studies that have compared the existing reperfusion strategies, thrombolysis (TL) and primary PCI (PPCI), made use of treatment regimens that since have been improved with the use of mechanical and medical adjunctives. The objective of this thesis was to compare both of these strategies employing updated regimens in accordance to current guidelines with respect to; 1) efficacy in restoring blood flow and myocardial perfusion, 2) clinical outcome and 3) cost-effectiveness.

Methods and results: Between November 2001 and May 2003, 205 patients with STEMI were randomized to PPCI with adjunctive abciximab or TL. The low molecular weight heparin enoxaparin was used as anticoagulant in both groups. In 42% treatment was initiated in the pre-hospital phase. The primary end points were the rate of ST-segment resolution (STRES) ≥ 50% 120 minutes after inclusion and the rate of normalized (TIMI 3) flow in the infarct related vessel 5-7 days after treatment, serving as surrogates for a beneficial outcome. Secondary end points were the ability to restore myocardial perfusion evaluated angiographically by TIMI Myocardial Perfusion Grade (TMPG) 5-7 days after inclusion in the study, clinical events at 30 days and one year cost-effectiveness.

The patients were followed prospectively for one year and, in addition, information on survival status and major clinical events was collected from national registries for an extended follow up period of a median of 5.3 years.

STRES≥ 50% was achieved in 68% following PPCI and 64% after TL (n.s.). However, the TIMI 3 rate was higher after PPCI compared to TL (71% vs. 54%, p=0.04). TMPG tended to be better in the PPCI group than in the TL group. An analysis of the evolution of TMPG in the PPCI cohort revealed that there was a significant improvement of myocardial perfusion in the week following PPCI. Thirty day mortality rates were low and similar in the groups.

At one year PPCI was tended to be less costly ($-2,505) than TL ($-2,505; n.s.), mainly due to higher costs for re-hospitalizations in the TL group. Primary PCI also lead to an insignificant gain in quality-adjusted survival (0.031 QALYs). A bootstrap analysis indicated that PPCI has a high probability of being cost-effective when a threshold value of $50,000 is employed.

A survival analysis at 5.3 years showed a significant benefit from PPCI in terms of the combination of all-cause death and recurrent infarction (p=0.03) as well as for cardiac mortality alone (p=0.02).

Conclusion: Primary PCI is more efficient than thrombolysis in re-establishing antegrade flow in the infarct- related artery and offers a better long term clinical outcome with respect to major cardiac events without an increase in societal costs. Thus, based on the conditions under which this study was performed, primary PCI is a more efficient alternative than thrombolysis for the treatment of ST-elevation myocardial infarction.

LIST OF PUBLICATIONS

This thesis is based on the following studies, which will be referred to by their Roman numerals.

I. Svensson L, **Aasa M**, Dellborg M, Gibson C.M., Kirtane A, Herlitz J, Ohlsson Å, Karlsson T, Grip L.

Comparison of very early treatment with either fibrinolysis or percutaneous coronary intervention facilitated with abciximab with respect to ST recovery and infarct-related artery epicardial flow in patients with acute ST-segment elevation myocardial infarction: The Swedish Early Decision (SWEDES) reperfusion trial. American Heart Journal 2006;151:798.e1-798.e7.

II. **Aasa M**, Kirtane A, Dellborg M, Gibson C.M, Prahl-Abrahamsson U, Svensson L, Grip L.

Temporal changes in TIMI myocardial perfusion grade in relation to epicardial flow, ST-resolution and left ventricular function after primary percutaneous coronary intervention. Coronary Artery Disease 2007;18:513-518

III. **Aasa M**, Henriksson M, Dellborg M, Grip L,Herlitz J, Levin L-Å, Svensson L, Janzon M.

Cost and health outcome of primary percutaneous coronary intervention versus early thrombolysis in acute ST-segment elevation myocardial infarction-results from the SWEDES trial. Submitted for publication.

IV. **Aasa M**, Dellborg M, Herlitz J, Svensson L, Grip L.

Sustained risk reduction for cardiac events after primary coronary angioplasty compared with thrombolysis for acute ST-elevation myocardial infarction: five-year results from the Swedish Early Decision (SWEDES) reperfusion trial. Submitted for publication.

CONTENTS

LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
AV	Atrio-ventricular
BP	Blood pressure
ΔC	Mean difference in cost
CABG	Coronary artery bypass grafting
C/E-plane	Cost-effectiveness plane
CI	Confidence interval
CTFC	Corrected TIMI frame count
DRG	Diagnose related group
ΔE	Mean difference in effect
ECG	Electrocardiogram
EpC	Epidemiologiskt centrum
EQ-5D	Euroqual-5 Dimensions
GP	Glycoprotein
ICD	International Statistical Classification of Diseases
I.V.	Intravenous
LAD	Left anterior descending artery
LBBB	Left bundle branch block
LCX	Left circumflex artery
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
Q	Quadrant
QALY	Quality adjusted life year
RCA	Right coronary artery
RR	Risk ratio
r-tPA	Recombinant tissue plasminogen activator
S.C.	Subcutaneous
SD	Standard deviation
SCAAR	Swedish coronary and angioplasty registry
STEMI	ST-elevation myocardial infarction
STRES	ST-segment resolution
SU	Sahlgrenska Universitetssjukhuset
SÖS	Södersjukhuset
TFG	TIMI flow grade
TIMI	Thrombolysis in myocardial infarction
TL	Thrombolysis
TMPG	TIMI myocardial perfusion grade
t-PA	Tissue plasminogen activator
UK	United kingdom
VS.	Versus

INTRODUCTION

Acute ST-elevation myocardial infarction (STEMI), i.e. an acute coronary syndrome (ACS) distinguished by an abnormal elevation of the ST-segment on ECG, is a clinical manifestation of an acute occlusion of a coronary artery. It accounts for approximately 30-45% of patients with ACS and is the sole manifestation of the acute coronary syndrome where rapid reperfusion has been proven to save lives [1-3] [4] by reducing infarct size and preserving left ventricular function.

Annually in Sweden approximately 35 000 people suffer from an acute myocardial infarction [5]. Out of 20 000 admissions into coronary care units in 2008, 7800 patients (37%) had either ST-elevation or left bundle branch block (LBBB) on their ECG rendering them eligible for reperfusion therapy [6].

The existing reperfusion strategies

The existing reperfusion methods are intravenous thrombolysis (TL), also denoted fibrinolysis, and primary percutaneous coronary intervention (PPCI), i.e. catheter-based coronary angioplasty with balloon dilation or related interventions. In addition, acute coronary artery bypass surgery may be offered in selected cases.

The advantage of thrombolysis is its wide availability. It can be offered to patients in rural districts far outside the catchment areas of centers with invasive facilities. Another advantage is that treatment can be given before arrival at hospital which can result in a shorter time delay between first contact with the medical system and the start of treatment.

The shortcomings of this method are the small but significant risk of major bleeding, especially in the elderly with low body weight, and a relatively high rate of failure in restoring normal coronary artery flow, which is the goal of the therapy.

The alternative reperfusion method, PPCI, implies an emergency coronary angioplasty, without preceding thrombolysis, in order to restore normal flow in the artery. PPCI is effective in securing and maintaining coronary artery patency and avoids some of the bleeding risks of thrombolysis. The disadvantages are the restricted availability as the method requires well-equipped coronary catheterization laboratories and trained operators and medical staff which can only be offered in selected centers and the inherent time-delay to treatment in comparison to TL. However, the recent

implementation of organized networks for PPCI in many countries has increased the availability and shortened the time PCI related time delay.

Reperfusion therapy from a historical perspective

The importance of intracoronary thrombosis.

The presence of thrombi at the site of occlusion has been known for more than a century. Whether intracoronary thrombosis was a causative factor behind STEMI or a consequence, i.e. thrombus formation caused by low or abolished blood flow secondary to myocardial tissue injury [7] , was a subject of debate until the early 1980s when angiographic studies during evolving infarction by DeWood and colleagues [8], and post-mortem studies by Davies and Thomas [9] and Falk[10] revealed the causative role of plaque disruption and coronary thrombosis.

We now know that approximately 2/3 to 3/4 of fatal coronary thrombi are precipitated by the sudden rupture of an inflamed, lipid-rich plaque covered by a thin fibrous cap[11,12]. After a complete coronary artery occlusion, myocardial infarction begins to develop after 15 to 30 minutes and progresses from the subendocardium to the subepicardium in a time-dependent fashion (the wave-front phenomenon)[13,14]. Re-establishing blood perfusion to the tissue, reperfusion, may save myocardium at risk from undergoing necrosis.

Despite the re-establishing of patency in an epicardial infarct-related artery, however, tissue reperfusion may in practice be prevented by distal embolization of thrombotic material leading to microvascular obstruction[15]. This has been clearly demonstrated on myocardial contrast echo and magnetic resonance tomography [16-19]. In coronary thrombosis, the initial flow obstruction is usually due to platelet aggregation, but fibrin is important for the subsequent stabilization of the early and fragile platelet thrombus [10]. Therefore, both platelets and fibrin are involved in the evolution of a persisting coronary thrombus.

Thrombolysis

In the 1960s and 70s, before the causative role of thrombosis was established, the concept of intravenous thrombolysis was investigated by several groups [20 21]. Despite

initial promising results, the regimens that were used with high doses of fibrinolytic agents administered over long periods caused high rates of bleeding complications which prevented these therapies from gaining wider acceptance.

With the recognition of the causative role of the occlusive thrombus in the evolvement of acute myocardial infarction intracoronary administration of fibrinolytics were tried with reported high rates of success [22,23]. However, this regimen was not considered feasible as it required access to catheterization laboratories and skilled operators. The positive experiences from these studies lead to the development of more modern strategies with the short-term and high dose intravenous administration of fibrinolytic agents.

In the mid-1980s the first mega-trials, applying a regimen with intravenous streptokinase, convincingly showed a reduction in mortality by a mean of 18% compared with placebo [2-4]. The ISIS-2 study also proved the importance of aspirin in the context of thrombolysis. A further development was the discovery of the fibrin-specific tissue plasminogen activator (tPA) in 1984. The GUSTO-1 study showed a marginal benefit of tPA compared with streptokinase in terms of mortality [24] and defined the role of heparin adjunctive to aspirin and fibrinolytics, thereby setting the general standard for modern thrombolytic therapy.

Primary PCI

For the first 15 years following its introduction, coronary angiography was generally considered unsafe and contraindicated in the early phase of acute myocardial infarction (AMI). That did not however prevent Rentrop from performing the first primary angioplasty in1979 [25], only two years after Andreas Gruentzig had performed the first angioplasty in man.

In 1980 De Wood and colleagues were the first to demonstrate that emergency cardiac catheterization in the acute phase of myocardial infarction was feasible and not associated with an apparent increased risk of complications [8]. Soon after, in 1982, Meyer and colleagues successfully performed balloon angioplasty after clot dissolution with intracoronary streptokinase [26] and, later the same year, Hartzler and co-workers introduced primary PCI as an alternative strategy for achieving myocardial reperfusion. As for intracoronary fibrinolysis, the lack of a wide availability of catheterization facilities restricted the use of PPCI for many years.

Further development of pharmacological strategies

Various clinical trials have subsequently evaluated adjunctive medication and treatment strategies for thrombolysis.

The longer half-life of the modified tPA recombinant tissue-type plasminogen activators (r-tPA) that allow for bolus administration have shown an efficacy equivalent to accelerated tPA [27,28] and their ease of administration has subsequently made them the standard thrombolytic agents in use today.

The low molecular weight heparin, enoxaparin, has been shown to have an antithrombotic effect that is superior to unfractionated heparin when combined with a plasminogen activator with a small but significant increase in major bleeding [29-31].

Knowing the role of intracoronary thrombosis in STEMI and the potential risk of thrombin-initiated platelet activation, researchers went on to investigate combinations of a reduced dose of fibrinolytics and potent anti-platelet drugs in order to increase the efficacy of thrombolysis.

Initial studies, which were not powered for mortality, showed that the combination resulted in a superior flow in the infarct related artery in comparison with fibrinolytics alone. This came however at the expense of increased bleeding complications [32]. The largest trials published regarding tPA fibrinolytics in combination with the glycoprotein (GP) IIb/IIIa receptor blocker abciximab that addressed mortality did not, however, show any significant benefit of the combination [29,33]. There were fewer ischemic complications after initial reperfusion, but this benefit did not result in any reduction in mortality and the incidence of bleeding complications was increased.

Thienopyridines in addition to aspirin and fibrinolytics have been proven to be beneficial by reducing the incidence of reinfarctions [34,35] and have become the latest addition to the armamentarium.

Pharmacological thrombolysis or primary PCI?

The first randomized comparative studies between intravenous thrombolysis and primary PCI appeared in the early 1990s, 10 years after the introduction of primary PCI.

In these trials, balloon angioplasty was compared with streptokinase or tPA. Although they could show promising results from the invasive point of view they were not powered to detect any significant differences in short-term mortality [36-38].

In the mid-1990s the larger GUSTO IIb [39] trial failed to show any significant reduction in in-hospital mortality by PPCI compared with thrombolysis as, also, did the DANAMI-2 [40] and PRAGUE-2 [41] studies that were initiated in the late 1990s. In all these studies, however, there were consistent reductions in the incidence of recurrent ischemia and recurrent infarctions favoring primary PCI.

Since then, a meta-analysis of 23 randomized trials comprising a total of 7739 patients has been performed [42]. In the included trials, fibrin-specific agents were used in the majority (15) but stents and GP blockers were only used in a minority (12 and 8 respectively out of the 23 trials). In this meta-analysis, primary PCI was superior in terms of short-term mortality (7 vs. 9%), non-fatal reinfarction (3 vs. 7%), stroke (1 vs. 2%), and their composite (8 vs. 14%).

Mortality in STEMI

Prior to the advent of coronary care units in the 1960s, AMI associated in-hospital mortality averaged 25–30% [43]. The prethrombolytic era of the mid-1980s saw an average in-hospital fatality of 18% [44].

With the widespread use of fibrinolytic drugs and adjunctive therapy such as aspirin, anticoagulants, and later on coronary interventions in-hospital mortality has since been reduced to 4-13% in a number of European registries [45].

The latest European Heart Survey, published in 2006, reports a 30 day mortality rate of 7.2% [46] and the Swedish national registry reports a 6.2% in-hospital mortality [45] in patients diagnosed with STEMI.

Despite the significant reduction in mortality that has been observed over the last few decades, due not only to earlier diagnosis and reperfusion treatment but also to improved management of complications as well as secondary prophylaxis (with aspirin, beta-blockers, ACE inhibitors and statins), myocardial infarction remains a major public health problem and a leading cause of mortality in developed countries.

Current recommendations and status of reperfusion therapy

Provided that PPCI can be performed within 90 [47] or 120 [48] minutes after first medical contact, it has been the preferred therapeutic option in international guidelines since 2003/04 [49,50].

In the absence of contraindications, and if primary PCI cannot be performed within the time limits, pharmacological reperfusion should be initiated as soon as possible and be followed by coronary angiography within 24 hours after successful thrombolysis.

Rescue PCI should be performed in the case of thrombolysis failure, particularly in high-risk patients.

Facilitated PCI, i.e. pharmacological reperfusion delivered prior to planned PCI, is currently not recommended.

At present, 3/4 of STEMI patients under the age of 80 receive reperfusion therapy in Sweden. Among them, nine out of ten are subjects for PPCI [6]. The high usage of PPCI has been made possible thanks to the expansion of PCI-capable facilities and the organization of pre-hospital facilities within local hospital networks during the last decade.

There is, however, a great heterogeneity in patient access to reperfusion therapy and the modality of reperfusion worldwide. According to a recent report, reperfusion therapy is still underused in many European countries with rates varying from 37 to 93%. Furthermore, thrombolysis remains the dominating strategy in one third (8 out of 24) of the European countries that report to national registries on management of STEMI patients [45] and it is estimated that thrombolysis is still used in one quarter of STEMI patients in the United States.

Thus, there remains, even in developed parts of the world, a great need for guidance on how to implement and organize reperfusion therapy in the setting of STEMI.

The underlying arguments for yet another comparative study

At the end of the 1990s the strategies for thrombolysis and primary PCI had evolved compared with the strategies used in the earlier studies. The bolus type of tPA (r-tPA) had replaced streptokinase and unfractionated heparin (UFH) had been replaced by enoxaparin as an anticoagulant agent in connection to thrombolysis. Furthermore, there

were strong indications that pre-hospital was superior to in-hospital thrombolysis and this had become increasingly utilized thanks to the establishment of pre-hospital organizations [51,52].

The use of stents had decreased the rate of early abrupt reocclusions and reinfarctions[53,54]and the adjunctive use of abciximab had been shown to improve epicardial flow [55] and myocardial perfusion [56,57]and reduce the incidence of ischemic complications [53,55]. A more recent meta-analysis has also indicated a beneficial effect on survival [58].

The consistent use of these adjunctive pharmaceuticals and strategies had not been evaluated in any comparative study, thus mandating further studies in which up-dated regimens of the therapeutic strategies were used.

Surrogate endpoints

The ultimate endpoint in comparative studies on reperfusion therapy is mortality. This would, however, require enrolment of a large number of patients. Depending on the studies one chooses to base a sample size calculation upon, the required number of subjects needed to detect a significant, and clinically meaningful, difference in short-term (30 days) mortality would be in the order of 2500 to more than 4000 subjects. This in turn requires a large-scale study which would not be feasible for most organizations.

One way to approach the problem is to measure a marker intended to substitute for a meaningful clinical endpoint. Such a surrogate endpoint is a measure of effect of a certain treatment that not only correlates with but also shows a relationship to a clinically meaningful endpoint.

The ultimate goal of reperfusion therapy is to reduce mortality by reducing the myocardial injury through re-establishing antegrade myocardial flow and tissue perfusion. Thus, measures of antegrade flow and tissue perfusion would serve as meaningful surrogates in this respect.

Blood flow in the infarct-related artery

A semiquantitative measure of blood flow in a coronary artery is the TIMI flow grade (TFG) classification[59] that has been successfully used to assess coronary blood flow in

acute coronary syndromes. It is a valuable tool for comparing the efficacy of reperfusion strategies and in the identification of patients with a higher risk of adverse outcome, including mortality [60,61].

A method to further quantify TIMI flow is the Corrected TIMI Frame count (CTFC)[62,63] and this parameter may serve as a more objective index of coronary flow than the TIMI flow classification.

Myocardial perfusion

Restoration of antegrade flow in an epicardial infarct related artery does not, however, necessarily lead to the restoration of tissue-level perfusion[16].

Myocardial perfusion can be interrogated angiographically. In the classification system developed by Gibson et al, the TIMI perfusion grading (TMPG 0-3)[64]is based on the kinetics of the contrast agent entering and exiting the myocardial microvasculature. A patient with TMPG 0/1 is interpreted as having a microvasculature that failed to open after reperfusion (closed myocardium), while a patient with TMPG 2/3 has a perfused (open) myocardium. The rightness of this categorization is supported by studies using myocardial contrast echocardiography [65].

Restoration of TMPG 2/3 is a powerful independent determinant of myocardial salvage [66] and is associated with improved survival in patients presenting with cardiogenic shock [67]. Furthermore TMPG adds independent prognostic information to epicardial flow and permits risk stratification even among those with normal antegrade flow in the infarct related artery (TIMI 3 flow)[68].

TFG, CTFC and TMPG have typically been evaluated shortly after reperfusion and there is little information on the evolution of these indices thereafter.

ST-segment resolution

In several studies ST-segment resolution on ECG (STRES) has been able to predict the risk of death and heart failure in patients treated with thrombolysis[69 70,71].

Lack of STRES, despite attainment of TIMI 3 flow, is associated with a larger infarct size and an increased mortality risk[72,73].

It has been suggested that while TMPG reflects mechanical patency of the microvasculature and the integrity of the endothelium, STRES may reflect the functional status of the supplied myocardium[74]. Measures of both parameters appear to be independent and complementary in their prognostic significance[75-77].

Health economic evaluations

The health system, like many other sectors in society, is facing a reality characterized by limited resources and seemingly endless demands. Decision makers have to decide how constrained resources are to be used to maximize health outcomes. Economic analyses play an important role, serving as an aid in achieving these goals. All reperfusion strategies carry costs associated with expensive pharmacological compounds, devices, equipment and the establishment of complex organizations to handle these therapies. Thus in applying these methods it is of fundamental importance to evaluate costs and resource utilization with regards to achieved benefits in terms of reductions in mortality and morbidity.

In STEMI, thrombolysis offers good efficacy at a relatively low cost compared to accepted therapies in other fields of medicine. The introduction of primary PCI seems to bring additional benefits at a higher initial cost. Data from previous health economic evaluations indicate that PPCI offers better health outcomes with similar costs over a 6-12 month perspective[78,79]. Coronary stents or GP IIb/IIIa receptor blockers were, however, not used in these studies and costs outside of the health care system were not included. This justifies a cost-effectiveness analysis in which updated regimens of both therapies are compared and societal costs are included.

AIMS OF THE THESIS

The objective of this thesis was to compare existing strategies for reperfusion therapy in acute ST-elevation myocardial infarction with respect to:

efficacy of restoring myocardial perfusion

short- and long-term clinical outcome

cost-effectiveness

PATIENTS AND METHODS

The Swedish Early Decision (SWEDES) Reperfusion trial

Organization and inclusion

The trial was planned in 2000-2001 and was conducted in mainly urban areas of southeastern Stockholm, Örebro county and greater Gothenburg including the areas of northern Halland and northern Älvsborg.

Out of the seven participating hospitals Sahlgrenska Universitets sjukhuset/Sahlgrenska, Södersjukhuset (SÖS), Örebro Universitetssjukhus and Norra Älvsborgs Länssjukhus had on-site cardiac invasive facilities while the remaining hospitals (Varbergs sjukhus, Sahlgrenska Universitetssjukhuset/Östra and Mölndal) lacked such facilities.

In order to make pre-hospital enrolment possible, the study also involved their respective affiliated ambulance organizations. Ambulances were staffed with nurses and/or paramedics trained in intravenous drug administration.

Study population

Enrolment started in November 2001 and ended in May 2003. Patients of >18 years of age presenting within six hours after the onset of symptoms, with a duration of >30 minutes and a ST-segment elevation of >2 mm in at least two adjacent precordial leads or >1 mm in at least two adjacent limb leads were considered for inclusion.

Among exclusion criteria were conventional contraindications for thrombolysis, known renal insufficiency, a body weight of >120 kg, or cardiogenic shock defined as a systolic blood pressure of <90 mm Hg in combination with cerebral deterioration and peripheral coldness. Initially there was no upper age limit but in July 2002 one corresponding to 75 years was introduced. This was dictated by the results of the ASSENT-3 PLUS study [29], which indicated that the antithrombotic regimen used in our study may be deleterious in an old age population. Details of inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria.
Continuous symptoms for ≥ 30 min.
Duration of symptoms ≤ 6 hours
ST-segment elevation ≥ 2 mm in at least 2 adjacent precordial leads or ≥ 1mm in at least 2 adjacent limb leads

Exclusion criteria.
Initially no upper age limit, from July 2002 age > 75 years
Age < 18 years
Women of childbearing potential not using contraceptives
Cardiogenic chock defined as systolic blood pressure <90 mm Hg combined with cerebral deterioration and peripheral coldness
Cardiopulmonary resuscitation lasting for >10 min within 2 weeks prior to inclusion
Blood pressure above 180/110 at any time
Major surgery or trauma within 6 weeks
Puncture of a non-compressible vessel within 24 hours
Gastrointestinal bleeding within 6 months
Previous stroke or cerebral haemorrhage
Bleeding from urinary tract within 6 months
Known allergy to study drugs
Use of GP IIb/IIIa receptor inhibitor within 7 days
Body weight > 120 kg
Known renal insufficiency (s-creatinine >200 mmol/l)
State of confusion making it impossible to obtain informed consent
Language difficulties or other logistic problems
Any disease that implies a significant risk of death within one year

Randomization and study protocol

Patients were considered for enrolment after a rapid clinical assessment and application of a checklist of inclusion and exclusion criteria. This was carried out either by the ambulance staff or the attending physician at the local hospital, depending on how the first medical contact was established. The decision to include a patient was always made by a physician at the randomizing hospital after evaluation of the ECG recorded on-site and transmitted via the wire-less telephone system to the hospital.

Patients were allocated a treatment strategy after opening a sealed envelope (envelope method) chosen in consecutive order at the randomizing hospital. Furthermore, randomization was stratified by centers in blocks of 10 to ensure a balanced distribution of treatment groups. In patients in both groups, study medications were administered as soon as possible after randomization and, if applicable, in the pre-hospital setting.

Patients randomized to thrombolysis were then taken to the nearest coronary care unit and treated according to current routine. In case of enrolment in the pre-hospital setting or at a hospital without an invasive facility, patients in the primary PCI group were directed to the nearest center equipped with an invasive facility for immediate coronary angiography followed by PCI if appropriate.

The study protocol stated that a coronary angiography should be performed prior to discharge, preferably 5-7 days after randomization, unless the patient had undergone an unscheduled angiography prior to that.

Study drug regimens

Study drug regimens for both groups are shown in table 2. Aspirin was given to all patients who were not on continuous treatment as a loading dose of 300-320 mg orally, followed by 75 mg daily. A loading dose of 300 mg of clopidogrel was given in connection to PCI in patients that had received a stent. All other medications were given at the discretion of the physicians in charge of the patient.

Table 2. Study drug regimens

	Primary PCI	Thrombolysis
Aspirin	300-320 mg orally	300-320 mg orally
Enoxaparin	0.75 mg/kg body weight i.v.	30 mg i.v. + 1 mg/kg body weight s.c. every12 hours during hospital stay
Reteplase		10+10 U i.v. with a 30 min interval
Abciximab	0.25 mg/kg body weight i.v. + 10µg/min i.v. for 12 hours	
Clopidogrel	300 mg + 75 mg daily for 30 days after stent implantation	

Coronary angiography and primary PCI

Coronary angiography was performed as soon as possible after the arrival of the patient at the catheterization laboratory. The procedure was carried out via a femoral artery using a standard Judkins technique followed, if indicated, by immediate PCI. No further anticoagulation other than that stated in the study protocol was administered. The use of thrombus aspiration and other mechanical devices was left to the discretion of the operator. If appropriate, implantation of bare metal stents was encouraged.

Angiographies obtained in connection to any PCI and at 5-7 days after randomization were preceded by an intra-coronary injection of nitroglycerine and acquired with a

frame rate of 25 frames/second from specified angles in order to optimize the conditions for the angiographic evaluations.

Revascularization policy

If the diagnostic angiography obtained in connection to primary PCI revealed other coronary lesions than the culprit lesion identified by ECG, a general recommendation was not to treat them unless the clinical state of the patients dictated otherwise. In such cases, a patient was to be considered for a staged procedure or coronary by-pass grafting for prognostic reasons in a stable condition.

Rescue PCI and non-scheduled procedures were to be considered if a patient showed signs of failed thrombolysis or ischemia at rest. In patients in whom the pre-discharge angiography revealed a significant lesion in the infarct-related artery, it was recommended not to treat the lesion unless the patient had anginal symptoms or had demonstrated ischemia prior to this.

Evaluation of ST-elevation resolution

STRES was evaluated by the Ischemia Core laboratory, Sahlgrenska Universitetssjukhuset/Östra, Gothenburg, Sweden.

ECGs were recorded at inclusion in the study, and at 60, 90 and 120 minutes thereafter. The lead showing the largest ST-elevation (worst lead) was used for analysis. ST-elevation at the J-point+60 ms was measured and the mean of three consecutive beats was recorded. All ECGs were evaluated by two independent reviewers in a blinded fashion and the mean of their results was used.

Criteria for exclusion from analysis were a QRS duration of >120 ms, AV-block of 2nd degree or higher, ventricular rhythm or ECGs of inadequate quality making an evaluation impossible.

ST-elevation resolution was calculated according to the formula:

$$\frac{\text{ST-elev}^{\text{incl}} - \text{ST-elev}^{120\ \text{min}}}{\text{ST-elev}^{\text{incl}}} \textbf{ x 100 = \% STRES}$$

Angiographic evaluations

All coronary angiographies that were obtained during the index hospitalization were evaluated by an angiographic core laboratory (TIMI/Perfuse Angiographic Core laboratory, Boston, MA, U.S.) with reviewers blinded to all clinical data. Angiographies were evaluated with respect to TFG, CTFC and TMPG in the infarct-related territory.

Per protocol and alternative analyses

The per protocol analysis was based on the 144 patients who underwent a coronary angiography prior to discharge. Thirty-eight patients had an angiography earlier during the hospital stay and, as a consequence, were not candidates for a pre-discharge angiography.

To compensate for the loss of data two additional analyses were conducted.

The first alternative analysis (alt. 1) was based on the first angiography after reperfusion therapy, excluding the post-intervention angiography connected to the primary PCI procedure in the PPCI group.

The second alternative analysis (alt. 2) was based, when available, on follow-up angiographies. For patients without pre-discharge angiography the last angiography regardless of indication was used, excluding the post-intervention angiography in connection to the primary PCI in the PPCI group. In this analysis post-procedure angiographies connected to rescue or emergent PCI in the TL group were included.

TIMI flow grade

The qualitative TFG classification system [59]was used for the assessment of blood flow in the infarct related epicardial artery. The system classifies coronary flow into four grades where grade 0 denotes no antegrade flow and grade 3 denotes normal antegrade flow. Details of the classification system are shown in **Table 3.**

Table 3. Definitions of the TFG and the TMPG Systems

Grade	Characteristics
TFG, a grading system for epicardial coronary flow	
0	No perfusion; no antegrade flow beyond the point of occlusion
1	Penetration without perfusion; the contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run
2	Partial reperfusion; the contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed is perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the culprit vessel (eg, the opposite coronary artery or coronary bed proximal to the obstruction)
3	Complete perfusion; antegrade flow into the bed distal to the obstruction occurs as promptly as into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery
TMPG, a grading system for myocardial perfusion	
0	Dye fails to enter the microvasculature; there is either minimal or no ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit artery indicating lack of tissue level perfusion
1	Dye slowly enters but fails to exit the microvasculature; there is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (approximately 30 seconds between injections)
2	Delayed entry and exit of dye from the microvasculature; there is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (ie, dye is strongly persistent after 3 cardiac cycles of the washout phase and either does not diminish or only minimally diminishes in intensity during washout)
3	Normal entry and exit of dye from the microvasculature; there is the ground glass appearance ("blush") or opacification of the myocardium in the distribution of the culprit lesion that clears normally, and it is either gone or only mildly/moderately persistent at the end of the washout phase (ie, dye is gone or is mildly/moderately persistent after 3 cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), similar to that in an uninvolved artery; blush that is of only mild intensity throughout the washout phase but fades minimally is also classified as grade 3

Corrected TIMI frame count

CTFC was used to quantify the flow rate in the infarct related artery. In the CTFC method [62] the number of cine frames required for the contrast agent to reach a standardized distal coronary landmark in the culprit vessel is counted using an electronic frame counter. Normal flow is defined as ≥14 frames to <28 frames.

The distal landmarks selected for the analyses in the respective vessels were:

in the right coronary artery (RCA), the first branch of the posterolateral artery, in the circumflex system (LCX), the most distal branch of the obtuse marginal branch which includes the culprit lesion and in the left anterior descending artery (LAD), the most

distal apical branch (the "whales tail"). To correct for the longer length of LAD, the number of frames for this artery were divided by 1.7 to arrive at the CTFC.

In case of an occluded artery, a frame count of 100 was imputed which represents the 99th percentile for frame counts among open arteries in a STEMI setting.

TIMI myocardial perfusion grade

Perfusion of the myocardium was evaluated by use of the TMPG classification system [64]. This method evaluates the timing of the entrance and exit of the contrast agent into the microvasculature in the downstream myocardium.

In a normal myocardium the contrast agent enters and exits the microvasculature briskly, which gives a ground glass appearance of the myocardium ("blush") when the contrast passes through.

In case of impaired myocardial perfusion, the contrast agent either fails to enter the microvasculature, or there is an abnormally slow entrance and exit (staining). In the present study, we further categorized TMPG 0-1 as "closed myocardium" and TMPG 2-3 as "open myocardium" as has been described by Gibson [80]. A description of the TMPG grading system is shown in Table 3 and examples of TMPG 0 and 3 are shown in figure 1.

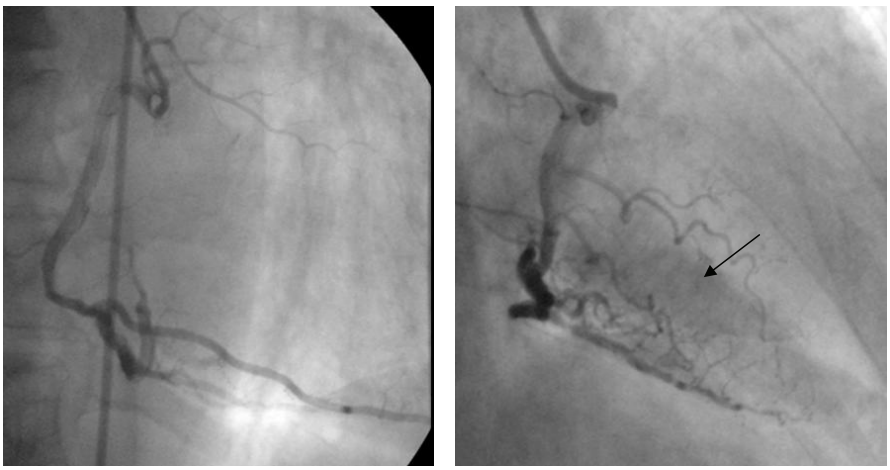

Figure 1. Right anterior oblique views of the right coronary artery (RCA) showing examples of TMPG 0 (closed myocardium) to the left, and TMPG 3 (open myocardium) to the right. "Blush" is indicated by an arrow.

Health economic evaluation

General considerations

Measuring health outcome

In all types of economic evaluations the general approach is to compare costs and consequences of an intervention with the costs and consequences of an alternative intervention. While the measurement of costs is principally similar between different types of economic evaluations, the way consequences are measured may vary. One can measure health effects in natural units such as units of blood pressure reduction, avoided myocardial infarctions or lives saved [81].

In our evaluation we have chosen to express health outcome as quality-adjusted life years (QALYs) gained and the result of the evaluation could be expressed as cost per QALY gained. The advantage of using QALY as health outcome is that it simultaneously incorporates gains from reduced morbidity (quality gains) and mortality (quantity gains) and integrates them into a single measure. Hence it is possible to compare QALY gains from different therapeutic areas since treatments that mostly influence quality of life can be compared with those that mainly influence mortality. Furthermore, QALYs have the advantage of integrating gains (e.g. improved survival) with potential drawbacks (e.g. reduced quality of life due to side effects) of treatments. A quality adjustment weight, also referred to as a utility, is based on patient preferences, the more preferable a health state, the more utility (higher quality adjustment weight) is associated with it. Quality adjustment weights are measured on a scale between 0 and 1, where 0 corresponds to death and 1 corresponds to full health.

In calculating QALYs, a quality adjustment weight of being in a particular health state is multiplied by the time spent in that state. The results are then summarized over the study period. Quality adjustment weights are usually derived from questionnaires that are either disease-specific or generic (generalized non disease-specific). In the present study we have chosen to use the generic Euroqol-5 Dimensions (EQ-5D) questionnaire [82] which is a simple-to-use, self-administered questionnaire that provides a valid assessment of general health status. It is, furthermore, systematically characterized and reference values of a norm population are available. For our purposes it was more valuable than a disease specific instrument (e.g. the Angina Pectoris Quality of Life Questionnaire) as there are other symptoms than angina that might be limiting in the post-infarction period.

Approach of the health economic evaluation

In estimating the costs of alternative therapies, two main approaches are available.

In gross-costing, aggregate costs such as charges based on the hospital billing system, cost by Diagnose related group or cost data from datasets or medical literature can be used. When an economic evaluation is conducted alongside a clinical trial, such as in this case, a micro-costing approach can be used. In a micro-costing approach resource quantities are collected during the trial at a detailed level. This is potentially more precise than the gross-costing approach but often more demanding as it requires a larger number of different resources to be identified, measured and allocated a unit cost.

The present evaluation is performed on a within-trial basis and does not include any extrapolation of costs and health outcomes beyond the duration of the trial. Accordingly, costs for added years of life or costs related to loss of productivity due to premature death are not accounted for. Furthermore, some costs outside the health care sector such as costs related to formal and informal home care were not accounted for in the analysis. However, societal costs generated by sick-leave benefits during the study period are included.

Use of resources and assignment of unit costs

Data on the use of health care resources were prospectively collected during the one year study period. Resources accounted for were categorized as hospitalizations, investigations, revascularization procedures, pharmaceuticals, and outpatient visits. Visits to primary care givers were not included.

Unit costs were either based on average prices (investigations except from coronary angiographies, outpatient visits), market prices (pharmaceuticals) and average procedure costs (coronary angiographies, revascularization procedures) or estimated on an average cost model per day (hospitalizations in different types of wards). The cost model per day includes fixed costs for facilities and equipment, caregiver salaries (physicians, nurses etc.), laboratory tests, ECGs, ward supplies and catering etc. The calculation of the average procedure cost (angiographies, revascularizations) was based on all procedures performed during a time period in the two largest hospitals participating in the study (SU, SÖS) and, as a result, the average cost includes the additional cost of procedures carried out during out of office hours.

To account for costs outside of the health care system, the number of days of sick-leave was recorded and costs were calculated as the number of days off work multiplied by the average daily labour costs stratified by sex.

Quality of life assessment

In order to obtain health state scores (quality adjustment weights) to calculate quality-adjusted survival, the patients were asked to answer the Euroqol-5 Dimensions (EQ-5D) questionnaire [82]on three occasions during the study period: within three days of randomization (index hospitalization), at one month and at one year. The EQ-5D questionnaire consists of five questions/attributes that cover patient mobility, self-care, usual activities, pain/discomfort and mood. Each attribute has three levels of severity (no problem, moderate problem or major problems). Hence, 243 unique health states are defined with the EQ-5D. The different health states were scored by use of the UK EQ-5D index tariff [83,84] in order to obtain quality adjustment weights for each of these health states. Quality adjustment weights for each time period (index hospitalization to 1 month and 1 month to 1 year) were calculated using the mean of the two measurement points. The means for the time periods were then multiplied by the fraction of a particular period that a patient was alive.

The cumulative quality-adjusted survival was finally calculated by adding up the values for each time period taking into account the length of each. The maximum number of QALYs for a patient is 1 (alive with full health during the one-year follow-up) and the minimum number of QALYs is 0 (dying more or less immediately after randomization).

Long term outcome: data extraction from national registries

Information on survival status, cause of death, readmission in hospital and revascularization procedures was retrieved from the National Patient Registry, the National Cause of Death Registry (EpC, National Board of health and Welfare, Stockholm), the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), and the National Registry of Thoracic Surgery (Uppsala Clinical Research Center, Uppsala). Survival confirmation was performed by crosschecking with the Swedish National Population Registry.

Data were retrieved in May 2009, and by then complete information was available up to 31 December, 2007. Cause of death was categorized as cardiac or non-cardiac according to pre-specified criteria. Cardiac causes of death include all manifestations of ischemic heart disease and complications following acute myocardial infarctions (ICD codes I 20.0-I 25.9), heart failure (I 50.0-I 50.9), ventricular arrhythmias (I 47.2, I 49.0), cardiac arrest including sudden cardiac death (I 46.0-I 46.9), and other sudden death (R 96).

Statistics

Sample size calculation

Power and sample size calculations for the underlying clinical study were made with respect to the expected outcomes regarding the primary endpoints, rate of ST-resolution of ≥50% at 120 minutes after randomization, and rate of TIMI 3 flow 5-7 days after inclusion. The sample size calculation was based on the assumption that PPCI would lead to a reduction of therapeutic failure by 50% in terms of ST resolution (from a 40% to 20% failure rate) and by 65% in terms of TIMI 3 flow (from a 30% to 10% failure rate) compared with TL. With a power of 80% regarding ST resolution, 90% regarding TIMI 3 flow and a significance level of 0.05 (2-sided test), a total of 180 patients would be required. To cover for losses it was decided to randomize 200 patients in the study.

Statistical analysis

All comparisons between treatment assignments were performed on an intention-to-treat basis. Continuous variables are presented as medians (with 25^{th} and 75^{th} percentiles) or as means ± SD. For dichotomous variables, the chi-squared and Fischer exact tests were used to test for differences. In some analysis differences were expressed as risk ratios (RR) with 95% confidence intervals. Continuous variables were compared using Student's t-test. For repeated measures data the Mann-Whitney U test was used when variables were continuous and the McNemar chi-squared test was used for binary variables.

In the health economic evaluation, data on cost and quality-adjusted survival were expressed as means and compared by using Student's t-test. In order to investigate the robustness of the parametric assumptions underlying the Student's t-test, the result from a bootstrap procedure was used for comparison.

Survival analysis was performed by use of the Kaplan-Meier product limit method. The significance of the differences between treatment groups was tested with the Log-rank test and expressed as hazard ratios with corresponding 95% confidence intervals obtained from univariable Cox proportional hazard regression analyses. In analyzing survival from cardiac death and its composite, patients who experienced death from non-cardiac causes where censored. For multivariable adjustment of important baseline characteristics, Cox regression was employed. Follow-up time was reported as the median (with 25th and 75th percentiles) and computed with the reverse Kaplan-Meier method where the outcomes "death" and "censored" are reversed, and the median time to censoring is used [85].

All *P* values are 2-sided without any correction for multiple comparisons.

Bootstrap analysis and the cost-effectiveness plane

On cost data

Patient-level cost data are usually highly positively skewed with a pile-up of costs on the left of the distribution. This is because costs are naturally bounded by zero but they have no logical upper bound. It is common to have a small portion of patients with very high costs, reflecting a complicated clinical course. If a standard statistical approach was to be used the preferable summary measure would be the median cost that might be evaluated using non-parametric methods. However, in the context of cost in an economic evaluation this is inappropriate given that decision-makers need to be able to link the summary measure of cost per patient to the overall budget impact and this can only be achieved using the mean. The non-normality of costs means that confidence intervals from standard methods (t-test or OLS regression) may not be valid which makes a comparison of mean costs unreliable.

The non-parametric bootstrap method

The method of non-parametric bootstrapping [86,87] can provide confidence intervals for the difference in mean costs between two groups in case of non-normality.

Bootstrapping is a resampling procedure (which implies randomly drawing a sample from an original data set and replacing it before the next sample is drawn) that

estimates an empirical sampling distribution for the statistic of interest rather than relying on parametric assumptions.

Applied on our data, the bootstrap approach involves the following steps:

A sampling with replacement of 101 cost/effect pairs from the patients in the PPCI group followed by a calculation of the mean cost and effect in this bootstrap sample

A sampling with replacement of 101 cost/effect pairs from the patients in the TL group followed by a calculation of the mean cost and effect in this bootstrap sample

A calculation of the difference in cost between the groups and the difference in effect between the groups by using the bootstrapped means from the steps above.

This three-step procedure provides one bootstrap replication of the mean differences in cost and effect.

In the present study the process was repeated 5000 times and the result was a vector of bootstrap replicates of the differences in mean cost and effect between the groups, which represents the empirical estimate of their sampling distribution. This allowed for the calculation of their confidence intervals.

It is important to understand that the procedure implies that samples of the same size as the original data are drawn with replacement from the original sample. As a consequence, no more data are added into the analysis.

In the present analysis, the bootstrapped cost data was used to check the robustness of the parametric assumptions underlying the Student's t-test, i.e. the difference in mean costs with corresponding confidence intervals from the bootstrap analysis was compared to the results from the parametric analysis.

In addition, the bootstrapped cost difference and effect difference pairs were used to assess the uncertainty of the cost-effectiveness analysis by plotting them on the cost-effectiveness (C/E) plane and evaluating the distribution of the point estimates.

The cost-effectiveness plane

In the C/E plane[88] the x-axis is the mean difference in effectiveness measured as quality-adjusted survival (ΔE) and the y-axis is the mean difference in cost (ΔC) between the groups (PPCI minus TL)(Figure 2).

The interpretation of an estimate falling in quadrant (Q) II or IV is intuitive. In quadrant II PPCI is more effective and less costly than TL, i.e. PPCI dominates TL. In quadrant IV the opposite is true. In quadrant I increased effectiveness is achieved at increased cost. In this situation, the decision to adopt the new therapy will depend on whether the estimate lies below the acceptable threshold ratio for the willingness to pay. Quadrant III represents a situation where reduced effectiveness is associated with lower cost.

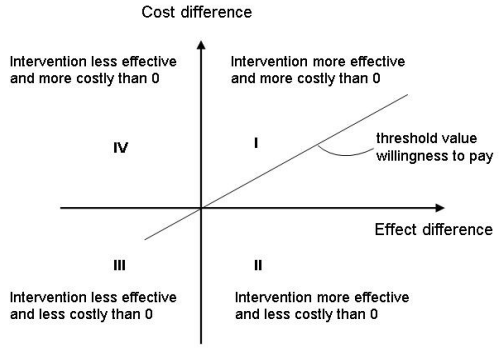

Figure 2. The C/E-plane. The horizontal axis represents the difference in effect between the intervention of interest and the relevant alternative and the vertical axis represents the difference in cost. Adopted from Black 1990 [89].

RESULTS

Logistics and background demographics

There were none or only marginal differences in the distribution of background characteristics between the two groups (Table 4). Forty-five percent of the patients were above 65 years of age and 19 % were older than 75. At presentation, 7% of the patients in the PPCI group and 4% in the TL group demonstrated Killip class >1 (p=0.40).

Randomization and initiation of therapy took place in the pre-hospital phase in 43% in the PPCI group and 41% in the TL group. There was no significant difference in terms of baseline characteristics between the pre- and in-hospital recruited patients. Among patients that were randomized before hospital admission, there were no deaths or bleeding complications and only one cardiac arrest (ventricular fibrillation) occurred.

Median time from onset of symptoms to thrombolysis was 114 minutes (83,197) and from onset of symptoms to balloon dilatation 202 minutes (154, 276). Median times from randomization to thrombolysis or PPCI were 12 minutes (10, 18) and 78 minutes (63, 101) respectively, which results in a PCI related delay of around 65 minutes.

Table 4. Baseline characteristics

	Primary PCI n=101	Thrombolysis n=104
Age, mean ± SD (years)	65.3 ± 10.9	64.3 ± 12.4
Men/women (%)	74/27	78/26
History of previous:		
Angina pectoris (%)	19	16
Myocardial infarction (%)	13	16
Heart failure (%)	2	3
Hypertension (%)	32	29
Diabetes mellitus (%)	14	11
CABG (%)	4	2
PCI (%)	6	7
Current smoker (5/5)* (%)	29	29
Pre-hospital initiation of treatment(%)	43	42
Anterior wall myocardial infarction (%)	42	38

Clinical outcome

Clinical events

Killip Class >1 at any time during index hospitalization was noted in 24% in the PPCI group and in19% in the TL group (p=0.50).

In-hospital and 30 day mortality rates were low and similar in both groups and there was no significant difference regarding the composite endpoint death or recurrent infarction either (Table 5). Three patients in the TL group suffered a stroke during index hospitalization.

Table 5. Clinical events at 30 days, one year and during the total follow-up period

Cumulative number of patients experiencing:	Primary PCI n=101	Thrombolysis n=104	p
Myocardial infarction			
30 days	0	2	0.50
One year	4	7	0.54
Total follow-up	9	18	0.10
Death			
30 days	3	4	1.00
One year	5	8	0.57
Total follow-up	11	19	0.17
Cardiac death			
30 days	3	3	1.00
One year	3	6	0.50
Total follow-up	3	12	0.03
Death or non-fatal myocardial infarction			
30 days	3	6	0.50
One year	9	14	0.38
Total follow-up	19	33	0.04
Stroke			
30 days	0	3	0.25
One year	0	4	0.12
Total follow-up	6	8	0.78
PCI excluding primary PCI	15	64	<0.001
CABG	8	19	0.04
Any revascularization excluding primary PCI			
30 days	7	59	<0.001
One year	15	72	<0.001
Total follow-up	22	79	<0.001

At one year there were still no significant differences between the groups, but at five years significantly fewer patients in the PPCI group had experienced the composite of death or recurrent infarction and the single end point death by cardiac causes. There was also a trend towards a lower overall mortality in the PPCI group. This was solely attributed to a very low incidence of cardiac deaths in the PPCI group, whereas the incidence of non-cardiac deaths was the same.

A Kaplan-Meier survival analysis with a median follow-up time of 5.3 (5.0, 5.8) years confirmed the differences between the groups seen in crude event rates (Figure 3). After adjustment for important background factors PPCI remained significantly associated with a favorable outcome in terms of cardiac mortality and its composite, while the association with the composite end point all-cause mortality or recurrent infarction weakened to a trend.

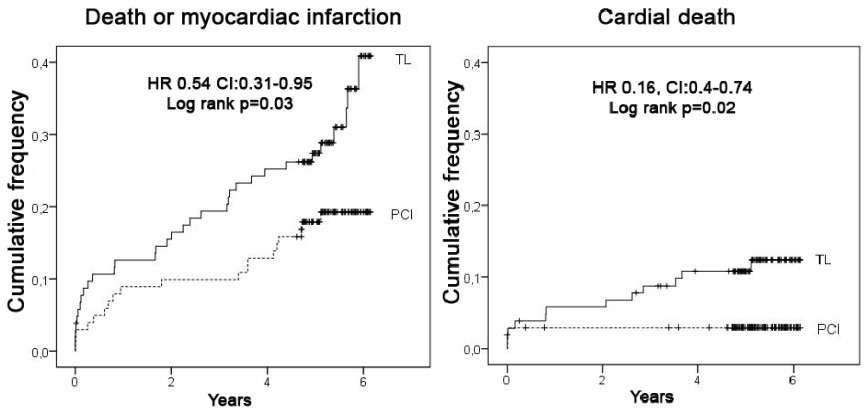

Figure 3. Cumulative rates of all-cause death or recurrent myocardial infarction (left) and cardiac death (right) in relation to treatment group. The vertical lines on the event curves denote censored cases.

Furthermore, the event curves continue to separate over time which could indicate a sustained risk reduction that lasts well beyond the early post-infarction period.

When the survival analysis was stratified in pre-hospital and in-hospital start of treatment, the result indicates that the benefit of PPCI is restricted to patients in whom treatment was started after arrival at hospital, while there was no difference between the groups in patients where treatment was started in the pre-hospital setting. This finding must be interpreted with caution, however, as we found no significant interaction between treatment group and where treatment was started, although there was a trend for it.

Hospital re-admissions.

The rate of hospital re-admissions due to angina during the total follow-up period tended to be lower in the patients randomized to PPCI (28% vs. 38%, p=0.10) while no difference or trend was seen in terms of readmissions due to heart failure (7% vs. 4%, p=0.37).

Revascularizations.

Revascularization procedures following the initial reperfusion treatment (primary PCI or thrombolysis) were more frequent in the TL group in which 23% of the patients had rescue PCI and 27% had PCI due to recurrent ischemia or PCI in connection to the pre-discharge angiography at 5-7 days after randomization.

After a median of 5.3 years of follow-up, 79/104 patients in the TL group and 22/101 patients in the PPCI group had undergone a revascularization procedure (p=<0.001). In both groups the majority of revascularizations occurred during the first month following randomization (Figure 4). CABG was more frequent in the TL group (19/104 vs. 8/101, p=0.04).

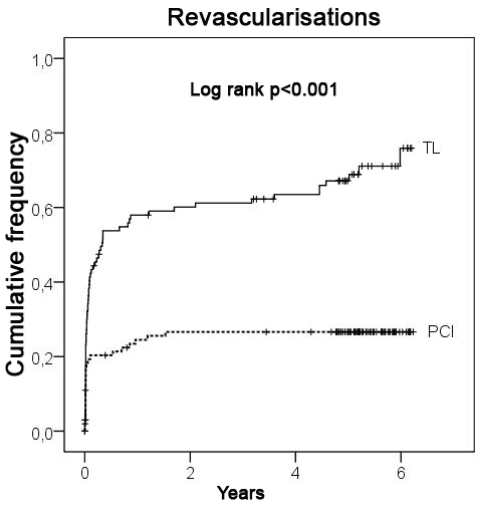

Figure 4. Cumulative rates revascularization procedures in relation to treatment group. The vertical lines on the event curves denote censored cases.

Surrogate end points

Loss of data

ECG recordings suitable for evaluation of STRES at 120 minutes after randomization were available in 149 out of 205 patients. The patients that were excluded from the analyses due to insufficient data did not differ from the analyzed patients in terms of baseline demographics. They had, however, a significantly higher mortality rate at all time points (Table 6).

Angiographies obtained as per protocol at 5-7 days after randomization and used in the primary analyses were available in 144 out of 205 patients. The reason for lost data was primarily that patients had undergone a coronary angiography prior to this and hence were no longer candidates for a repeat angiography. Other reasons were patient refusal and death.

Table 6.

	STRES			**Angiographic evaluation**		
	Excluded n=56 n (%)	Included n=149 n (%)	p	Excluded n=64 n (%)	Included n=141 n (%)	p
Age mean ± SD (y)	64.5+/-12.1	64.9+/-11.6	0.85	64.2+/-12.6	65.0+/-11.3	0.64
Male gender	43(77)	109(73)	0.72	46(72)	106(75)	0.61
Previous history of:						
Angina pectoris	7(13)	28(19)	0.40	11(17)	24(17)	1.00
Myocardial infarction	7(13)	22(15)	0.82	9(14)	20(14)	1.00
Heart failure	1(2)	4(3)	1.00	2(3)	3(2)	0.65
Hypertension	15(27)	46(31)	0.61	16(25)	45(32)	0.41
Diabetes mellitus	5(9)	20(13)	0.48	11(17)	14(10)	0.17
CABG	1(2)	5(3)	1.00	1(2)	5(4)	0.67
PCI	2(4)	11(7)	0.52	6(9)	7(5)	0.23
Confirmed myocardial infarction	51(91)	144(97)	0.14	56(88)	139(99)	0.002
Killip class >1 during index hosp.	14(25)	30(20)	0.45	18(28)	26(18)	0.14
Death within 30 days	5(9)	2(1)	0.02	7(11)	0	<0.001
Death within 5 years	14(25)	16(11)	0.014	14(22)	16(11)	0.06
Cardiac death within 30 days	5(9)	1(1)	0.006	6(9)	0	0.001
Cardiac death within 5 years	8(14)	7(5)	0.03	7(11)	8(6)	0.24

The patients that were excluded from this analysis had the same baseline characteristics as those included except for a lower rate of confirmed myocardial infarction (Table 6)

and, for obvious reasons, all in-hospital mortality was found in this group as the angiography was performed prior to discharge. The result of the analyses of surrogate end points is shown in Table 7.

Table 7.

	PPCI	TL	p
STRES ≥ 50% at 120 min (75/74)*	51(68)	47(64)	0.56
Primary angiographic analysis: (79/65)*			
TFG	56(71)	35(54)	0.04
cTFC median(25^{th}, 75^{th} percentile)	31(22,41)	36 (27,51)	0.03
TMPG	48(61)	32(50)	0.17
Alternative angiographic analysis 1: (n=81/97)*			
TFG	57(70)	46(48)	0.002
TMPG	49(60)	41(42)	0.02
Alternative angiographic analysis 2: (n=81/97)*			
TFG	58(72)	55(57)	0.049
TMPG	49(60)	42(43)	0.03

Results are given as n (%).
*Number of analyzed patients in the 2 treatment groups, respectively.

Epicardial flow

TIMI 3 flow immediately after primary intervention was present in 76% of the patients randomized to PPCI.

Significantly more patients in the PPCI group had TIMI 3 flow on the per protocol angiography 5-7 days after reperfusion therapy compared with the TL group (71% vs. 54%, RR 1.31, 95% CI 1.00-1.72, p=0.04). The difference in favor of PPCI was sustained in the alternative analyses. Accordingly, CTFC was significantly lower in the PPCI group (31 (22, 41) vs. 36 (27, 51), p=0.03).

Myocardial perfusion

ST-segment resolution

Myocardial reperfusion assessed with ST-segment resolution at 120 minutes did not differ between the groups. The rate of >50% ST-resolution was 68% in the PPCI group and 64% in the TL group (RR 1.07, 95% CI 0.85-1.35p=0.56). Neither was there any significant differences at any other pre-specified time point (60, 90 or 240 minutes).

Angiographic assessment

In the primary analysis there was a trend towards more patients in the PPCI group having "open myocardium" (TMPG 2-3) than in the TL group (62% vs. 50%, p=0.15) (not a primary endpoint and not presented in the paper).

In the alternative analyses that were made to compensate for loss of data myocardial perfusion was, however, significantly better after PPCI than after thrombolysis (alt.1: 60% vs. 42%, p=0.02 and alt. 2: 60% vs. 43%, p=0.03).

The evolution of TMPG within the first week after reperfusion was studied in the PPCI cohort. In this group there was a significant increase in the incidence of "open myocardium" from 41% immediately after primary PCI to 61% at angiography 5-7 days later (p=0.003). Furthermore, improvement of perfusion was primarily seen in patients with STRES ≥50% at 120 minutes.

In conclusion, when reperfusion of the myocardium was assessed by STRES in connection to reperfusion therapy, the groups did not differ significantly. However, an angiographic evaluation one week later indicated that myocardial perfusion was restored to a higher degree after PPCI than after TL. Whether perfusion improves within the first week after TL, as was seen after PPCI, is unknown.

Due to the large amount of missing data and the additional survival bias we were not able to make a reliable evaluation of the prognostic value of the surrogate end points as was originally intended.

Health economic evaluation

In a one year perspective the total cost per patient was $25,315 in the primary PCI group vs. $27,819 in the thrombolysis group. The mean difference of -$2,504 in favor of PPCI was not statistically significant (95% CI: -8,168-3,160, p=0.38). The non-parametric bootstrap analysis resulted in a mean difference of -$2,466 (95% CI: -8,061-3,060) which showed that the parametric assumptions underlying the cost calculations could be accepted.

In the PPCI group the initial higher cost attributed to primary interventions and pharmaceuticals were counterbalanced by subsequent costs of more frequent re-hospitalizations and revascularization procedures after index hospitalization in the TL group. There were no significant differences in the use of other resources.

Regarding effectiveness, mean quality-adjusted survival was 0.759 in the PPCI group and 0.728 in the TL group. The mean difference of 0.031 QALYs was not statistically significant.

Thus, primary PCI was associated with trends for lower total costs (-$2504) and gain in health outcomes (0.031 QALYs).

To further investigate the uncertainty of the estimates, the 5000 bootstrap replicates were plotted on the C/E-plane (figure 5). This demonstrates that PPCI is less costly and more effective in 67% of the bootstrap replications, and that PPCI is cost-effective in 88% of the replications when a conventional threshold value of $50,000 per QALY is employed.

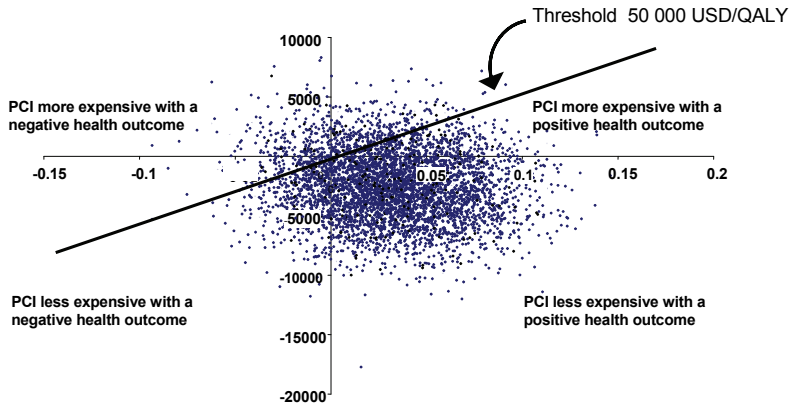

Figure 5. The figure shows a C/E-plane plot of cost and efficacy estimates based on the result of a non-parametric bootstrap analysis. A line representing a threshold of $50,000 for willingness to pay for an additional QALY is inserted.

DISCUSSION

The clinical study that formed the basis of this thesis was originally intended to serve as a pilot study for a larger national trial on reperfusion therapy in STEMI.

As a consequence, surrogate markers were used as efficacy measures and the study was therefore not powered for hard clinical events, not even over a long-term perspective. Accordingly there is an amount of uncertainty regarding the results on clinical outcome. Nevertheless, the combined findings regarding the ability to restore flow in the infarct-related artery, the long-term clinical outcome and the cost-effectiveness analysis all point in the same direction, namely that primary PCI is more efficacious than thrombolysis without an increase in societal costs. These findings are in line with the results from meta-analyses and studies on long-term outcome and cost-effectiveness [42,78,79,90-96].

Study design

The study aimed at comparing optimal strategies for reperfusion therapy as defined by recent (at the time the study was planned) well-conducted clinical trials. An effort was made to make use of updated regimens of both strategies in terms of adjunctive medication and modern PCI techniques as well as the use of pre-hospital organizations to shorten time delays to treatment.

When the regimens that were used are compared with current guidelines, one can conclude that they are still generally valid. Since our study was designed, however, early administration of clopidogrel, regardless of reperfusion strategy, and the use of thrombus aspiration devices in connection to primary PCI have been added into the guidelines based on the results of more recent studies. In the present study, clopidogrel was restricted to primary PCI patients and administered after PCI for the duration of one month and thrombus aspiration was performed in selected cases in approximately one third of the patients.

The role of low-molecular-weight heparin (LMWH) in the primary PCI setting is still unknown. There is support for enoxaparin in a recent prospective registry study where enoxaparin was associated with a significant reduction of the combined end point in-hospital death or recurrent infarction compared with UFH [97]. However, awaiting larger randomized studies, UFH remains the standard heparin in current guidelines.

Furthermore, at the time when the study was conducted drug-eluting stents (DES) were not available. In recent studies DES have been shown to reduce the need for target lesion revascularizations but have failed to demonstrate an impact on mortality after primary PCI for STEMI [98].

Despite that the median time delays from first medical contact to initiation of reperfusion therapy tended to be longer than generally observed today, they are within the recommended limits of 30 minutes to TL and 90 minutes to PPCI.

A strength of the present study is that it combines strategies from different previous studies in this field. Thus, patients were randomized and treated at first medical contact and, as a consequence, treatment was initiated in the pre-hospital setting in more than 40% of the patients, thereby reflecting a "real life practice" which has not previously been investigated. Previous studies have been focused on either in- or pre-hospital reperfusion strategies.

Surrogate endpoints

The analyses of the surrogate endpoints were hampered by missing data from a substantial proportion of the patients. As a consequence, the study did not reach the goal set by the sample size calculation and hence was underpowered with respect to the primary endpoints. This problem is, however, not unique to our study. The proportion of ECGs excluded from analysis in previous studies in this field is in the same range[99,100]. In the ASSENT-3 study ECGs from 44% of the patients were excluded.

Furthermore, these problems are enhanced by a survival bias which is obvious when analyzing clinical outcomes in the patients that were part of the analysis compared with patients for whom data were missing. Thus, the event rate in patients in the analysis of STRES was very low, even at five years, as half of the events occurred in the one quarter of all patients who had missing ECG data. Certainly this bias adds to the power problems.

Regarding the angiographic evaluation, survival bias was even more pronounced as the evaluation was made prior to discharge, thus excluding patients who died or suffered a serious complication during their stay in hospital.

ST-segment resolution

There are some points that need to be addressed concerning the methodologies used in the assessment of myocardial perfusion. The STRES concept was primarily developed and validated in studies evaluating efficacy of thrombolysis. The method has since been adopted into studies of primary PCI.

However, the usefulness of STRES in PPCI has been challenged by a recent report from the DANAMI-2 study that indicates that while STRES is an important prognosticator after thrombolysis it may be overemphasized as a surrogate endpoint after PPCI [101]. In that study, as well as in our study, STRES was evaluated at fixed time points after inclusion in the study, which is reasonable in studies comparing the efficacy of different reperfusion strategies.

Other studies on PPCI have, however, evaluated STRES at fixed time points after completion of the PCI procedure, which may be reasonable from a reperfusion point of view [102]. The proper time point for evaluating STRES after PPCI is therefore not well defined.

More recently, post-procedural residual ST-segment deviation has been held up as a better ECG marker of post-interventional perfusion status by some authors based on the independence of the amount of baseline ST-elevation, and that it reflects the degree and extension of the residual ischemia more accurately than STRES does [103,104]. It correlates to infarct size and myocardial perfusion and has shown to be a better predictor of mortality than STRES .

Furthermore, the use of continuous ECG recording, starting from inclusion of the patient in the study, has the potential to reduce the amount of missing data and to assure that evaluations are made at the specified time points. It will also detect transient ECG changes during PPCI which may provide valuable prognostic information [105,106].

Coronary angiography analyses

Regarding the angiographic evaluations, we saw considerably lower rates of TIMI 3 flow and TMPG 2-3 (open myocardium) after PPCI compared with what has been achieved in other studies, despite the general use of abciximab in our study.

Many investigators have reported TIMI 3 rates of 90-95% post-PPCI and normalized myocardial perfusion in the range of 60-90%. This incongruence is not readily explained but the fact that in many studies angiographies were evaluated by the

operator or by other reviewers at the clinical site as opposed to a core laboratory certainly plays a role. The rate of agreement between clinical sites and an angiographic core laboratory blinded to all clinical data is poor or moderate in terms of TIMI flow [62]. The same most certainly holds true for the evaluation of TMPG.

In addition, some groups have defined TIMI grade 3 flow as opacification of the coronary artery within three cardiac cycles (e.g. the PAMI group). This methodological drift results in rates of normal perfusion that are approximately 10% higher than if the original definition of TIMI grade 3 flow is employed [107].

Clinical outcome

The clinical outcome in the study population in general was good. The five year mortality rate was around 15 % of which only half consisted of cardiac mortality. This can partly be attributed to the attention to adjunctive medication and a very active revascularization policy in the TL group. As for the patients in the PPCI group, very few cardiac events occurred, and the readmission rates for angina and heart failure were low.

The low cardiac mortality rate in the PPCI group resulted in a continuous separation of the event curves which indicates a sustained risk reduction that lasts well beyond the early post-infarction phase. This is in contrast to findings in previous studies where the benefit of PPCI has been restricted to the early post-infarction period with no further risk reduction beyond that stage, resulting in event curves running parallel.

Cost-effectiveness

Although the point estimate of differences in cost (incremental cost) and differences in effect (incremental effectiveness) indicated that PPCI is less costly and more effective than TL (dominated TL), there was substantial uncertainty regarding this estimate as the difference in cost as well as difference in effect were statistically non-significant.

The uncertainty concerning cost-effectiveness is determined by analyzing the joint distribution of incremental cost and incremental effectiveness on the C/E-plane. This was achieved by employing a non-parametric bootstrap technique. The analysis showed that PPCI was less costly and more efficient in 67 cases out of 100 and cost-effective in

88 cases out of 100, if we are willing to allocate $50,000 per QALY gained which represents a conventional threshold value for willingness-to-pay in most industrialized countries.

Hence, although there is considerable uncertainty around incremental costs and incremental effects, it is clear that PPCI has a relatively high probability of being cost-effective given that we are willing to pay $50,000 for a QALY.

In order to obtain information on cost-effectiveness over an even longer perspective decision analytic modeling is needed. In such modeling, the cost and health outcome collected within randomized trials are extrapolated to a long-term horizon.

Implications for future research

The collective experience from this and previous studies has implications for future research and development in this field.

In the present study, as well as in similar comparative ones, the patients with the highest mortality risk were excluded from enrolment. This was valid not only for patients presenting with cardiogenic shock, but also for patients with renal failure, high blood pressure, left bundle branch block, extreme old age and bleeding disorders. Patients with these characteristics have the highest mortality rates in registry studies and excluding them from randomized studies makes it very difficult to detect any significant benefits from new treatment strategies. This is certainly a reason for why no single comparative study has been able to show any mortality benefit from either strategy.

Thus, future studies need to focus on the patient groups that hitherto have been excluded from STEMI trials.

Future studies also need to focus on refining the PPCI strategy in order to improve myocardial reperfusion. Recent MRI studies have shown that no-reflow seen on angiography depends on the size of the infarct core, but probably to a larger extent an area of microvascular obstruction. More than half of the patients in one study demonstrated a considerable component of obstruction which is potentially preventable [108].

Thrombus aspiration in connection to PPCI has been shown to decrease the risk of downstream embolization of thrombotic material into the myocardium, thereby

improving ST- resolution and myocardial blush. There are two studies which indicate that the use of aspiration catheters also might improve clinical outcome [109,110].

Furthermore, results from smaller studies suggest that intracoronary administration of abciximab is superior to intravenous administration in terms of markers of myocardial reperfusion and infarct size [111,112]. This need to be confirmed in larger randomized trials and larger randomized trials on STEMI patients is underway [113,114].

One more path to take is to target the reperfusion injury that follows prompt reperfusion of the ischemic myocardium. Recent trials that addressed the opening of the mitochondrial transition pores with cyclosporine [115] or inflammation with FX06 [116] at the time of reperfusion have been able to demonstrate a reduction of infarct size. Another promising approach is to intervene with protein kinase C [47], an intervention that is currently being investigated in a large multicenter trial.

CONCLUSION

In comparison with thrombolysis, primary PCI is:

- more efficient in re-establishing antegrade flow in the infarct-related artery, although immediate myocardial reperfusion does not seem to be affected.
- followed by a lower rate of cardiac events over long time after the infarction and
- with high probability cost effective.

Thus, under the conditions under which this study was performed, primary PCI is a more efficient alternative than thrombolysis for the treatment of ST-elevation myocardial infarction.

There is, however, room for refinement of the primary PCI strategy in order to improve both coronary flow and reperfusion of the myocardium.

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