Early Risk Stratification, Treatment and Outcome in ST-elevation Myocardial Infarction

ERIK BJÖRLUND
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Abstract

We evaluated, in patients with ST-elevation myocardial infarction (STEMI) treated with thrombolytics, admission Troponin T (TnT), ST-segment resolution and admission N-terminal pro-brain natriuretic peptide (NT-proBNP) for early risk stratification as well as time delays and outcome in real life patients according to prehospital or in-hospital thrombolytic treatment. Also, baseline characteristics, treatments and outcome in patients enrolled in the ASSENT-2 trial in Sweden and in patients not enrolled were evaluated.

TnT (n=881) and NT-proBNP (n=782) on admission and ST-resolution at 60 minutes (n=516) in patients from the ASSENT-2 and ASSENT-PLUS trials were analysed. Elevated levels of NT-proBNP and TnT on admission were both independently related to one-year mortality. However, when adding information on ST-resolution (<¿50%) 60 minutes after initiation of thrombolytic treatment, TnT no longer contributed independently to mortality prediction. High and low risk patients were best identified by a combination of NT-proBNP and ST-resolution at 60 minutes.

We investigated consecutive STEMI patients included in the RIKS-HIA registry between 2001 and 2004, if they were ambulance transported and had received prehospital (n=1690) or in-hospital (n=3685) thrombolytic treatment. Prehospital diagnosis and thrombolysis reduced the time to thrombolysis by almost one hour, were associated with better left ventricular function and fewer complications and reduced the adjusted one-year mortality by 30% compared with in-hospital thrombolysis.

Prospective data from the RIKS-HIA registry on STEMI patients treated with thrombolytics were linked to data on trial participants in the ASSENT-2 trial of thrombolytic agents and used for direct comparisons. Patients treated with thrombolytics and not enrolled in a clinical trial at trial hospitals (n=2048) had higher risk characteristics, more early complications and twice as high adjusted one-year mortality compared to those enrolled (n=729). One major reason for the difference in outcome appeared to be the selection of less critically ill patients to the trial.

Keywords: Acute myocardial infarction, Thrombolysis, Troponin, Electrocardiography, Natriuretic peptide, Prognosis, Prehospital thrombolysis, Treatment delay, Mortality, Registry, Clinical trial

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LIST OF PAPERS

I. Admission Troponin T and measurement of ST-segment resolution at 60 minutes improve early risk stratification in ST-elevation myocardial infarction.

II. Admission NT-proBNP and it’s interaction with admission Troponin T and ST-segment resolution for early risk stratification in ST-elevation myocardial infarction.
   Accepted for publication in Heart, 2005.

III. Prehospital diagnosis and start of treatment reduce time delay and mortality in real life patients with ST-elevation myocardial infarction.
   Submitted

IV. Outcome of ST-elevation myocardial infarction treated with thrombolysis in the unselected population is vastly different from samples of eligible patients in a large-scale clinical trial.

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### ABBREVIATIONS

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMI</td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>ASSENT</td>
<td>ASsessment of Safety and Efficacy of a New Thrombolytic</td>
</tr>
<tr>
<td>CPR</td>
<td>Cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>CABG</td>
<td>Coronary artery bypass grafting</td>
</tr>
<tr>
<td>CCU</td>
<td>Coronary care unit</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>LBBB</td>
<td>Left bundle branch block</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-brain natriuretic peptide</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PHT</td>
<td>Prehospital thrombolysis</td>
</tr>
<tr>
<td>RIKS-HIA</td>
<td>Register of Information and Knowledge about Swedish Heart Intensive care Admissions</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-elevation myocardial infarction</td>
</tr>
<tr>
<td>“Thrombolysis”</td>
<td>=Fibrinolysis”</td>
</tr>
<tr>
<td>TIMI</td>
<td>Thrombolysis in myocardial infarction</td>
</tr>
<tr>
<td>TnT</td>
<td>Troponin T</td>
</tr>
<tr>
<td>VCG</td>
<td>Vectorcardiography</td>
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</table>
INTRODUCTION

Ischemic heart disease is a major cause of mortality and morbidity in the Western world. One of its manifestations is ST-elevation myocardial infarction (STEMI) where the implementation of thrombolytic treatment has represented a major treatment advance. The primary goal of thrombolytic treatment is to completely restore coronary blood flow in the infarct-related artery as quickly as possible in order to increase myocardial salvage and reduce mortality. However, there is considerable variability in mortality risk among STEMI patients treated with fibrinolytics. Early risk prediction is therefore of great importance for identification of high risk patients and selection of the most optimal treatment strategy. It is also important to identify low risk patients as early as possible to avoid unnecessary and costly treatments.

One important and modifiable determinant of mortality in STEMI is time from symptom onset to thrombolysis. Despite many years of medical advances in the treatment of STEMI the time from symptom onset to thrombolysis has remained at large unchanged, with a median of 2.5 to 3 hours. A prehospital treatment strategy compared with regular in-hospital thrombolysis has been shown to reduce time to thrombolysis with around one hour as well as reduce in-hospital mortality in randomised trials. There are, however, sparse data on time delays and outcome in real life patients treated with prehospital thrombolysis (PHT) compared with in-hospital thrombolysis.

In the last decades a large number of randomised clinical trials in cardiology have been performed, which constitute the evidence base for cardiovascular care guidelines. Questions have been raised about the representativeness of these trials with respect to the included populations. For example, several randomised clinical trials of fibrinolysis in STEMI have repeatedly demonstrated an impressively low mortality. In the most recently performed fibrinolytic trials mortality have been around 6% at 30 days and 8% at 1 year. In contrast, population based studies with unselected patients receiving fibrinolytic treatment for STEMI have reported an in-hospital mortality of 6-11% and one-year mortality of around 15%.
BACKGROUND

Definition and pathogenesis of STEMI

Myocardial infarction (MI) reflects cardiac myocyte cell death according to prolonged ischemia, caused by a sudden obstruction of the coronary blood supply, almost always caused by arteriosclerosis and super imposed thrombosis. In most cases (around 75%) the thrombus formation is initiated by rupture of a vulnerable plaque whereas plaque erosion may account for the rest. Depending on the degree of obstruction and collaterals, the clinical presentation can vary from unstable angina pectoris (UAP), non-STEMI and STEMI. In non-STEMI and UAP the thrombus is not completely obstructive and the corresponding findings on the electrocardiogram (ECG) vary from normal over T wave abnormalities to ST-depression.

In STEMI there is a complete coronary obstruction producing typically ST-segment elevation on the ECG. In addition, a new or presumed new left bundle branch block (LBBB) on the ECG also belongs to this entity. In the diagnosis of myocardial infarction (STEMI and non-STEMI) a typical rise (exceeding the 99th percentile of a control group) and fall of a biochemical marker is mandatory. The majority of patients presenting with ST-elevation finally develop myocardial infarction, although imminent myocardial injury can be avoided by spontaneous reperfusion or very early reperfusion treatment.

When a coronary occlusion produces sustained transmural ischemia it takes 15-30 minutes before irreversible myocardial damage starts from the subendocardium and progresses outwards. In animal models there has been no effect on infarct size with reperfusion after 6 hours of complete ischemia while in humans indirect measurements have indicated no myocardial salvage if thrombolytic treatment is started 5-6 hours after symptom onset. However, several circumstances may alter the time course of myocardial necrosis such as presence of collaterals, visualised at coronary angiography in one third of cases with STEMI. Pre-infarction angina have also been associated with less myocardial damage, higher left ventricular ejection fraction (LVEF) at follow up and subsequent lower mortality, the so called precondition phenomenon. Moreover, the dynamic situation at the site of the thrombus including thrombosis, thrombolysis and vasospasm could lead to intermittent spontaneous reperfusion. Another consequence of the dynamic situation at the thrombus is distal embolization from the thrombus, which
can result in microvascular obstruction that may inhibit successful myocardial tissue reperfusion despite a patent epicardial infarct related artery \(^{34,35}\).

Early risk stratification and prognosis in STEMI

There is considerable variability in mortality risk in patients with STEMI treated with fibrinolytics\(^{2}\). Early risk prediction is therefore of importance for identification of high risk patients for early therapeutic decisions and for clinical resource utilization. It is also important to identify low risk patients as early as possible to avoid unnecessary and potentially harmful and costly treatments.

For many years risk stratification of patients with STEMI was based on variables from the patients’ history, physical examination and ECG on admission. Variables such as age, previous medical history (previous infarction, diabetes), indicators of large infarct size (systolic blood pressure, heart rate, Killip class and infarct location (anterior versus inferior)) and time to treatment have been identified as important predictors of outcome\(^{5,36}\) (Figure 1). In recent years additional variables for early risk stratification in STEMI have been identified such as elevation of markers of myocardial damage (troponins), markers of myocardial dysfunction (brian natriuretic peptide) and the early resolution of the ST-segment elevation.

**Myocardial damage (troponins)**

Among markers of myocardial damage, the troponins, troponin T (tnT) or troponin I (tnI) are the most specific for myocardial cell injury and are therefore the recommended markers for diagnosis of myocardial infarction\(^{27}\). They are located in the thin filament of the contractile apparatus of both skeletal and myocardial myocytes. However, cardiac isoforms of tnT and tnI are expressed only in cardiac myocytes and released from the myocytes in response to myocardial necrosis irrespectively of the cause of necrosis\(^{37}\). After acute myocardial infarction (AMI), the initial rise of tnT occurs 3 to 4 hours after the ischemic cell injury resulting from a release of the cytosolic tnT pool (Figure 2). Thereafter, tnT is released continuously for several days resulting from intramyocardial protein degradation\(^{38}\) and can be elevated up to two weeks after an AMI. Several studies have shown an independent prognostic value of elevated tnT on admission in STEMI patients treated with fibrinolytics\(^{39-41}\). Even when treated with primary percutaneous coronary intervention (PCI), patients with elevated tnT or tnI levels on admission had a 3 - 4 times higher short- and long-term mortality\(^{42,43}\). Some possible reasons for the adverse outcome in patients with elevated admission tnT have been proposed such as longer symptom duration, larger infarct size and
subsequent lower LVEF and reduced effect of thrombolytic or primary PCI in restoring thrombolysis in myocardial infarction (TIMI) 3 flow.\cite{32,35}

### Table

<table>
<thead>
<tr>
<th>Z-score</th>
<th>Adjusted OR (95% CI)</th>
<th>30-day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 years</td>
<td>11.0</td>
<td>2.7 (2.2-3.2)</td>
</tr>
<tr>
<td>Killip class &gt;1</td>
<td>9.3</td>
<td>2.3 (1.9-2.7)</td>
</tr>
<tr>
<td>Heart rate &gt;100 bpm</td>
<td>7.7</td>
<td>2.3 (1.9-2.8)</td>
</tr>
<tr>
<td>Anterior MI or LBBB</td>
<td>6.1</td>
<td>1.6 (1.4-1.9)</td>
</tr>
<tr>
<td>Systolic BP &lt;100 mmHg</td>
<td>5.5</td>
<td>2.7 (1.9-3.8)</td>
</tr>
<tr>
<td>Time to tlys &gt;4 hours</td>
<td>4.0</td>
<td>1.4 (1.2-1.6)</td>
</tr>
<tr>
<td>Weight &lt;67 kg</td>
<td>3.7</td>
<td>1.4 (1.2-1.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.3</td>
<td>1.4 (1.2-1.7)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>2.8</td>
<td>1.3 (1.1-1.6)</td>
</tr>
</tbody>
</table>

**Figure 1** The most important clinical predictors on admission of 30-day mortality in STEMI, from the InTIME II trial by Morrow and colleges.\cite{36}

**Figure 2** Time course in ST-elevation myocardial infarction.

**Myocardial dysfunction (NT-proBNP)**

Brain natriuretic peptide (BNP) and the N-terminal part of its prohormone, NT-proBNP, are released from the cardiac ventricles in response to increased wall stress, but also to ischemia per se. BNP is regulated through gene expression and BNP can increase very rapidly to an appropriate stimulus (Figure 2). The physiologic action of BNP is performed by natriuresis, vasodilatation and inhibition of the sympathetic nervous system.
and renin-angiotensin system. As a result BNP is closely involved in the regulation of blood volume, sodium balance and blood pressure. BNP and NT-proBNP levels are increased in congestive heart failure and related to the degree of left ventricular dysfunction and outcome. Although the relative increase of NT-proBNP levels is more profound than BNP levels as a result of cardiac impairment, their clinical utility have been equal.

After AMI, BNP levels is increased markedly with a maximum value around 16 hours after admission. When measured 2 to 4 days after STEMI, NT-proBNP was independently related to left ventricular function, heart failure and mortality in a previous small study. Also, previous studies reported strong correlations between NT-proBNP and BNP levels measured one to five days after STEMI and left ventricular function, but a weak correlation if BNP was measured on admission. In contrast, with respect to predictive capacity, there was no difference when NT-proBNP levels were evaluated on admission or after 2 days following STEMI in a previous small study. Moreover, elevated levels of NT-proBNP and BNP on admission in STEMI have been strongly associated with adverse outcome in two recent studies. These studies, however, only evaluated short-term mortality.

**ST-segment resolution**

The optimal treatment goal with reperfusion therapy in STEMI is not only to restore the blood flow in the epicardial vessel, but also to obtain quality of the nutritive response to reperfusion at the cellular level, tissue level reperfusion. Evaluation of ST-segment resolution with continuous ST-monitoring or serial ECGs have been shown to be useful for monitoring of the dynamic process after thrombolytic therapy and to detect reperfusion status both at epicardial and tissue level. The advantage of continuous ST-monitoring with vectorcardiography (VCG) or continuous 12-lead ECG compared with serial ECGs is the ability to more precisely detect reperfusion status by visualising the true ST-peak, and also the stability of patency.

ST-resolution at 90 minutes of >50% from the maximal ST-elevation assessed with continuous ST-monitoring identified around 80-90% of the patients with a patent (TIMI 2-3 flow) infarct related artery (IRA) and <50% ST-resolution identified around 50-60% of those with occlusion. Thus, ST-resolution is a reasonable accurate predictor of IRA patency but inaccurate predictor of occlusion. Importantly, in patients with a patent infarct related artery defined as TIMI 3 flow, about 30% showed no tissue level reperfusion assessed with contrast echocardiography or myocardial blush, which correlated strongly with the extent of ST-resolution. Moreover, no ST-resolution compared with ST-resolution in patients with TIMI 3 flow has been associated with larger infarct size, lower LVEF and a higher mortality. Thus, although TIMI 3 flow compared with vessel occlusion yields a
mortality benefit, patients with TIMI 3 flow can be further risk stratified in relation to early ST-resolution. Accordingly, early ST-resolution provides strong prognostic information when assessed at different time points (60, 90 or 180 minutes after start of thrombolysis) and when using different cut-off levels (≤50%, <30%, 30-70% and ≥70%) and has been shown to be superior to TIMI-flow grade in predicting outcome.

However, the combination of admission nTnT and early ST-segment resolution for predicting risk has previously not been evaluated. Furthermore, the prognostic interaction of admission NT-proBNP and the early resolution of the ST-segment elevation have not been investigated. Also, the relations between these three variables in the early phase of STEMI have not been elucidated.

Acute reperfusion treatment of STEMI with special reference to the influence of time

Patients presenting with typical symptoms of myocardial infarction and ST-elevation or new LBBB should all receive acute reperfusion treatment with thrombolytics or primary PCI as soon as possible unless there are clear contraindications. Thrombolytic therapy is widely available and easy to administer but only two-thirds of the patients achieve optimal patency rates, around 45 to 60 minutes elapses between initiating of therapy to restoration of coronary blood flow and there is a risk of a fatal bleeding. In contrast, primary PCI is associated with higher patency rates and a lower risk of bleeding. However, for beneficial results of primary PCI, a high volume of patients are needed and thus commonly available only at large interventional centres. Hence, primary PCI is associated with more time consuming transportation and also longer in-hospital delays than thrombolytic treatment. Nonetheless, randomised trials have consistently showed that primary PCI compared with in-hospital thrombolysis is associated with better outcome and is recommended if available within 60 minutes versus immediate thrombolysis, although some registries with real life patients have reported equivalent results. However, in a recent randomised trial comparing prehospital thrombolysis with primary PCI there was no statistically difference in 30-day mortality or re-infarction according to treatment strategy. In addition, in patients randomised within 2 hours of symptom onset (PHT was associated with 55 minutes shorter time to treatment versus primary PCI in this group of patients), PHT showed a tendency toward lower 30-day mortality compared to primary PCI. This underlines the importance of time to reperfusion which has been shown to be an important predictor of outcome irrespective of type of reperfusion method. The beneficial effect on mortality of an earlier time to treatment with respect to thrombolysis is
exponential rather than linear, with most benefit if administrated within 2 hours of symptom onset. In fact, the well-known Boersma curve (Figure 3) should actually be shifted to the right with 45 to 60 minutes to more appropriately describe the relation between treatment delay and reduction in mortality, since most of the included trials in Boersma’s meta-analysis only had information on time from symptom onset to hospital admission or to randomisation. Thus, the famous “golden hour” should rather be “two golden hours”.

**Figure 3** Numbers of extra lives saved per 1000 patients treated with thrombolysis at different treatment delays by Terkelsen and colleges (with permission).

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Pat. (n)</th>
<th>OR (95% CI)</th>
<th>Prehospital better</th>
<th>In-hospital better</th>
</tr>
</thead>
<tbody>
<tr>
<td>MITI -93</td>
<td>360</td>
<td>0.69 (0.30-1.57)</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>EMIP -93</td>
<td>5469</td>
<td>0.86 (0.72-1.03)</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>GREAT -91</td>
<td>311</td>
<td>0.56 (0.25-1.23)</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Roth et al -90</td>
<td>116</td>
<td>0.80 (0.17-3.77)</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Schofer et al -90</td>
<td>78</td>
<td>0.46 (0.04-5.31)</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Castaigne et al -89</td>
<td>100</td>
<td>0.74 (0.14-3.86)</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Overall</td>
<td>6434</td>
<td>0.83 (0.70-0.98)</td>
<td>•</td>
<td>•</td>
</tr>
</tbody>
</table>

**Figure 4** Results of the included randomised trials of prehospital versus in-hospital thrombolysis on hospital mortality in the meta-analysis by Morrison and colleges.
Despite many years of medical advances the time from symptom onset to thrombolysis has remained at large unchanged, with a median of 2.5 to 3 hours\textsuperscript{7}. Different strategies have been proposed and tested to reduce time to thrombolysis. More than half of the total time from symptom onset to treatment consists of patients’ delay in seeking medical attention\textsuperscript{87, 88}. Thus, several media campaigns in reducing patient delay have been performed and although initially partly successful, a long-lasting reduction in patient delay have been more difficult to achieve\textsuperscript{89-91}. Another way to reduce treatment delay is to change hospital routines in order to reduce time from hospital arrival to initiation of thrombolysis. Especially when thrombolysis is incorporated in routine emergency department protocols and administrated directly at the emergency department, a reduced in-hospital delay have been achieved\textsuperscript{92, 93}. Furthermore, in a recent large US registry, the median in-hospital delay decreased from 60 to 38 minutes from 1990 to 1999\textsuperscript{94}. Nonetheless, other registries and randomised trials consistently report in-hospital delays of 40 to 60 minutes\textsuperscript{95-97}.

Prehospital diagnosis and start of treatment prehospitaly have until now been shown to be the most efficient way to reduce the total time delay to thrombolysis. A prehospital treatment strategy versus in-hospital thrombolysis has been shown to reduce time to thrombolysis with around one hour and to reduce in-hospital mortality by 17% in a meta-analysis of randomised trials\textsuperscript{8} (Figure 4). To start the treatment prehospitaly it is necessary to establish a prehospital diagnosis of STEMI, which requires an ECG and a patient history. This task can be managed by ambulance physicians, as in four of the six included trials in the meta-analysis by Morrison and colleges\textsuperscript{8, 11, 13} or by general practitioners\textsuperscript{12} or with the use of computer algorithms\textsuperscript{98, 99} or by physicians at the hospital with the use of telemedicine\textsuperscript{14, 28, 100}. The latter system for prehospital diagnosis and thrombolysis is used in Sweden, which started to be more generally implemented in 1999. The ambulances in Sweden are staffed with paramedics who are trained to send a prehospital ECG in patients with chest pain to the corresponding hospital’s coronary care unit (CCU) using telemedicine and to check inclusion and exclusion criteria for thrombolysis according to standardised protocols. A physician on call evaluates the ECG and checks inclusion and exclusion criteria together with the paramedics over the phone and decides whether to start thrombolytic treatment prehospitaly or not\textsuperscript{101, 102}. One disadvantage with PHT is that it requires that the patient uses ambulance transportation to the hospital, which is done only in about 35% to 65% of patients with acute chest pain or confirmed AMI\textsuperscript{93, 95, 103, 104}, although patients without ambulance transportation constitute a lower risk group\textsuperscript{95, 103}, who probably would gain less of an earlier treatment.

There are sparse data on time delays and outcome in real life patients treated with PHT compared with in-hospital thrombolysis. One recent small registry study in France\textsuperscript{104} reported that PHT showed a tendency toward
lower one-year mortality compared with in-hospital thrombolysis and primary PCI. However, there was no information on time from symptom onset to therapy according to treatment modalities. Also, one third of the patients with in-hospital thrombolysis were admitted to the hospital without ambulance transport and thus not directly comparable with the PHT treated group of patients.

Natural course in STEMI

The true natural course of AMI is difficult to assess mainly because of the high frequency of acute coronary death outside hospital, but also since silent infarctions are common and the definition of the event varies. Community studies have shown an overall 30-day mortality of around 30-50% in AMI of which about half of the deaths occur within 2 hours\textsuperscript{105}. Accordingly, about one third of patients with evolving AMI die before first medical contact\textsuperscript{106}. This high initial mortality appears to be similar over the last 30 years. In contrast, there has been a sharp decrease in mortality of those treated in hospital and the subsequent total death rates have decreased at the population level in most developed counties, which has been linked to improvement in coronary care\textsuperscript{105}. In pre-CCU era in the 1960s, in-hospital mortality was reported to be 25-30\%\textsuperscript{107} and in the pre-thrombolytic era in the mid 1980s it was around 18\%\textsuperscript{108}. The use of fibrinolytic drugs, aspirin and coronary interventions has further decreased mortality to around 6 \% at 30 days\textsuperscript{16-18} and 8-9\% at 1 year\textsuperscript{19, 20} in those eligible for participation in a clinical trial of fibrinolysis. However, patients eligible for thrombolysis with STEMI who do not receive acute reperfusion treatment for various reasons, have a much higher mortality\textsuperscript{21, 109}. Furthermore, population based studies with unselected patients treated with fibrinolytics have also reported higher mortality rates than in clinical trials of fibrinolytics with an in-hospital mortality of 6-11\%\textsuperscript{21, 22}. Long-term follow-up in this kind of population is less well documented, but one registry study reported an one-year mortality rate of 15\%\textsuperscript{23}. The reasons for the differences in mortality rates between patients treated with thrombolysis and not included in a trial of thrombolysis compared to those included are poorly elucidated.
AIMS

In a population of clinical trial patients with ST-elevation myocardial infarction treated with thrombolysis:

- To evaluate admission Troponin T and ST-segment resolution at 60 minutes, separately and in combination, for early risk stratification (paper I).
- To examine the relations between admission N-terminal pro-brain natriuretic peptide, admission Troponin T and ST-segment resolution at 60 minutes (paper I and II).
- To investigate the prognostic interaction of admission N-terminal pro-brain natriuretic peptide with admission Troponin T and ST-segment resolution at 60 minutes for early risk stratification (paper II).

In a population of consecutive unselected ambulance transported patients with ST-elevation myocardial infarction treated with thrombolysis:

- To evaluate time delays, complications, short- and long-term outcome according to prehospital diagnosis and thrombolytic treatment or in-hospital thrombolytic treatment (paper III).

In a population of patients with ST-elevation myocardial infarction treated with thrombolysis:

- To evaluate baseline characteristics, treatments, complications and short- and long-term outcome in patients enrolled in the ASSENT-2 trial of thrombolytics in Sweden and in patients not enrolled in the trial at the same hospitals or at hospitals not participating in the ASSENT-2 trial (paper IV).
METHODS

Patients

*Paper I and II*

To evaluate the prognostic importance and interactions of troponin T, ST-resolution and NT-proBNP (paper I and II), patients included in the ASSENT-2\(^{16}\) (ASsessment of Safety and Efficacy of a New Thrombolytic) and ASSENT-PLUS\(^{110}\) trials were studied. The ASSENT-2 trial was a prospective, worldwide multicenter trial in which 16949 patients with STEMI were randomised to a new single-bolus thrombolytic, tenecteplase or front loaded alteplase. The primary endpoint was all-cause mortality at 30 days and patients were recruited during 1997 and 1998. In the ASSENT-PLUS study, 434 patients with STEMI were included in Scandinavia and USA during 1999 to 2000 to evaluate efficacy and safety of dalteparin as an adjunct to alteplase compared to routine heparin treatment. The primary endpoint was TIMI flow at coronary angiography after 4-7 days.

In both studies inclusion criteria were symptoms of acute myocardial infarction within 6 hours of onset, ST-elevation $\geq 0.1$ mV in 2 or more limb leads, or $\geq 0.2$ mV in 2 or more contiguous precordial leads, or LBBB and age $\geq 18$ years. Exclusion criteria in both trials were the regular ones for thrombolytic trials including hypertension (>180 mmHg systolic or >110 mmHg diastolic), major surgery or trauma within 2 months, previous stroke or dementia, therapy with oral anticoagulants, sustained cardiopulmonary resuscitation and pregnancy\(^{16,110}\).

In the present substudies that included patients with ST-monitoring (paper I and a subgroup in paper II), patients had to have <30 minutes delay between thrombolysis and start of ST-monitoring and had to be monitored at least 70 of the first 90 minutes or 3 of the first 4 hours or 20 of the first 24 hours to be included in the ST-monitoring substudy. Patients with LBBB were also excluded from ST-monitoring.

In both trials, at certain Swedish study hospitals, were plasma samples available on admission and continuous ST-monitoring performed. Totally 1456 patients were enrolled in the ASSENT-2 and ASSENT-PLUS trials at Swedish hospitals out of which 881 had an admission tnT sample (with 8.6% one-year mortality) out of which 782 (with 8.4% one-year mortality) had an admission NT-proBNP sample available (Figure 5). Of 864 patients without
LBBB included for continuous ECG-monitoring, 112 (with 14.6% one-year mortality) were excluded due to time criteria (see above) or bad quality, and the remaining 752 patients had a one-year mortality of 6.6%. The 516 patients (386 from the ASSENT-2 and 130 from the ASSENT-PLUS trial) who had both admission tnT and ST-monitoring available constituted the study population for paper I. The 782 patients (568 from the ASSENT-2 and 214 from the ASSENT-PLUS trial) with admission NT-proBNP comprised the population for paper II.

Figure 5 Patient populations in paper I and II.

**Paper III and IV**

To evaluate time delays and outcome according to prehospital or in-hospital thrombolytic treatment (paper III) and clinical characteristics and outcome in patients enrolled or not enrolled in the ASSENT-2 trial (paper IV), patients recorded in the Register of Information and Knowledge about Swedish Heart Intensive care Admissions (RIKS-HIA) were used.

In paper III patients were included between January 1, 2001 and November 30, 2004 and during the registration period, 75 of Sweden’s 80 hospitals were contributing data to the registry. All ambulance transported patients younger than age 80 years with a diagnosis of AMI, treated with thrombolysis (prehospital or in-hospital) and with information on time from symptom onset to thrombolysis were included. Older patients were excluded because of increased risk of concomitant disease that might not be covered by the registered variables. When evaluating time delays, all patients with a diagno-
sis of AMI during the registration period were used to obtain as many patients as possible. In all other evaluations only patients with their first recorded admission for AMI during the registration period were used to avoid double counting of patients. A total of 9212 patients with their first recorded AMI between January 2001 and November 2004 were eligible (Figure 6). All PHT patients (n=2095) and 4081 patients with in-hospital thrombolysis had information on ambulance transportation and were transported with ambulance. Of these, 1690 PHT and 3685 in-hospital treated had complete data on time from symptom onset to thrombolysis. The corresponding numbers of patients with one-year follow-up were 1294 and 3162, respectively. When evaluating time delays, all AMI admissions were used and thus 1911 patients with PHT and 4328 with in-hospital thrombolysis, transported with ambulance, younger than age 80 and with data on time from symptom onset to thrombolysis were eligible.

![Diagram](image)

**Figure 6** Patient population in paper III.

In paper IV all patients between December 9 1997 and November 27 1998, which was the recruitment period for the ASSENT-2 trial, treated with acute revascularisation or thrombolysis and with AMI as the primary diagnosis were included. During this registration period, 60 of Sweden’s 81 hospitals were contributing data to the registry. Only patients with their first recorded admission for AMI during the registration period were included. The criteria for the diagnosis of AMI were standardised and identical for all
participating hospitals using the WHO criteria. The biochemical criterion was at least one measurement indicating twice the upper limit of normal of an appropriate biochemical marker (usually creatine kinase-MB concentration).

Data from all 939 patients included in the ASSENT-2 trial (see above) at Swedish hospitals that contributed data to RIKS-HIA, were used to identify the corresponding records in the RIKS-HIA database.

Figure 7 Patient population and comparison groups in paper IV.

There were 4246 patients recorded in RIKS-HIA that met the inclusion criteria for the present study (Figure 7). Of these, 4 patients were excluded because we had no information of vital status. All patients in both the RIKS-HIA (n=4242) and ASSENT-2 (n=939) databases had complete information on date of admission, age, hospital and sex and based on these variables a match number was calculated for each patient to identify the ASSENT-2 patients in the RIKS-HIA database. Seven hundred and twenty nine of the 939 ASSENT-2 patients could be identified in the RIKS-HIA database. Of the 210 ASSENT-2 patients who were not identified, 41 patients (with 15% one-year mortality) were not identified because they were recorded in RIKS-HIA with an event of AMI and enrolled in the ASSENT-2 study but with a
previous AMI during the registration period. Thirty patients were not identified because they had normal levels of peak creatine kinase-MB and were therefore not recorded in RIKS-HIA with a diagnosis of AMI. The remaining 139 (of 939, 14.8%) patients were not identified for unknown reasons with a one-year mortality according to the ASSENT-2 database that was similar compared to the 729 ASSENT-2 patients that were identified (8.1% versus 8.8%).

Finally, we excluded 501 of the 4242 patients in RIKS-HIA not belonging to the ASSENT-2 population because they were all treated with acute PCI or coronary artery bypass grafting (CABG). Thus, the final study population in the RIKS-HIA database (n=3741) divided into 3 groups comprised ASSENT-2 patients, non-trial patients at ASSENT-2 recruiting hospitals (non-A2) and at hospitals not participating in the ASSENT-2 trial (non-A2-Hosp) (paper IV).

Data collection (paper III and IV)

RIKS-HIA contains details of all patients admitted to the CCUs of participating hospitals. Information is reported on case record forms including 100 variables, which has been described in detail previously. Briefly, the register includes information on demographic data, previous cardiac disease, ambulance transportation (since 2001), time of symptom onset, time of arrival at emergency department and at the CCU, time of start of thrombolytic treatment, medication at entry, prehospital or in-hospital thrombolysis, echocardiography, LVEF (since 2001), treatments and major complications and procedures during hospital stay, discharge medications and diagnosis. In addition, in 2002 the registry started to collect data on time of ambulance arrival on scene and time of prehospital ECG transmission.

Source data verification is continuously performed, and in 1972 randomly selected computer forms from 38 hospitals, comprising 161280 variables, there was 95% agreement overall between the registered information and the source data in the patients’ records.

Previous history of stroke, congestive heart failure, peripheral artery disease and chronic pulmonary disease was obtained by merging with the National Patient Register, which includes diagnoses on all patients hospitalised in Sweden from 1987 and onwards.

All patients for whom data were entered into the RIKS-HIA database were informed of their participation in the registry and the long-term follow-up. The RIKS-HIA registry and its merging with other registries were approved by the National Board of Health and Welfare and the Swedish Data Inspection Board.
Blood samples for biochemical markers (paper I and II)

Venous blood samples were collected before start of thrombolytic and anticoagulation therapy. After centrifugation the EDTA-plasma samples were stored frozen at –70 C for central analysis of TnT and NT-proBNP.

TnT was analysed with the third-generation TnT assay on an Elecsys 2010 with a detection limit of 0.01 μg/L. The mean intraassay CVs were 7.9% and 3.1% in the range <0.05 μg/L and 0.05-0.15 μg/L, respectively, and the mean interassay CVs were 11.2% and 5.1%, respectively. A prospectively defined cut-off level of <0.1 μg/L was used based on previous evaluations of admission TnT in STEMI for risk stratification, which should not be confused with the cut-off level used for diagnosis of myocardial infarction.

NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche diagn.). The analytical range extends from 20 to 35000 ng/L. At our laboratory, the total CV was 3.3% (n=21) at a level of 209 ng/L and 3% (n=21) at a level of 7431 ng/L. A normal level of NT-proBNP (≤97.5 th percentile in a healthy population) according to age and gender has been shown to be: ≤65 years, ≤184 ng/L and ≤268 ng/L, and in those >65 years, ≤269 ng/L and ≤391 ng/L, in men and women, respectively.

ST-segment resolution (paper I and II)

Monitoring with continuous VCG or continuous 12-lead ECG started when thrombolysis was initiated and continued for 24 hours. These two ST-monitoring methods have previously been shown to identify the same risk-groups among patients with unstable angina or non-q-wave infarction as well as in patients with STEMI.

Continuous VCG was performed with the MIDA 1000 or Coronet systems (Ortivus Medical AB, Täby, Sweden) or with the HP-MIDA system (Hewlett Packard, Andover, MA, USA). These systems continuously collect electrocardiographic signals from eight electrodes placed according to Frank. The electrocardiographic complexes are averaged each minute to form mean VCG complexes in the three orthogonal leads X, Y and Z. ST-vector magnitude (ST-VM) is calculated from the formula: ST-VM=(Xi^2+Yi^2+Zi^2)½, representing the total spatial ST-segment shift from the baseline. Xi, Yi and Zi are the magnitudes of ST-deviation in leads X, Y and Z, respectively. ST-VM is presented on-line on a computer screen as a trend curve. ST-segment changes were measured 60 ms after the J-point.

Continuous 12-lead ECG was performed using the ST-guard system (GE medical System, Information Technologies, Milwaukee, USA). This system continuously collects data from all 12 leads and, every minute this data is averaged over the last 10 seconds of each minute. From these averages, a ST-trend for each lead is constructed, stored and displayed on-line. ST-
analyses were made on the worst lead, defined as the lead showing the highest initial ST-elevation. ST-segment changes were measured at J-point + (1/16 x R-R interval), corresponding to J-point + 60 ms at a heart rate of 62.5 beats per minute.

The ST-trends were analysed by two blinded and independent observers at either the ischemia Core-laboratory, Sahlgrenska University Hospital/Östra, Göteborg, Sweden (VCG), or Uppsala University Hospital, Uppsala, Sweden (continuous 12-lead ECG). Differences in interpretation were solved by consensus, or by a third person if consensus could not be reached.

A cut-off level of \(<50\%\) ST-segment resolution from the maximal ST-elevation, measured at 60 minutes after start of recording, was used\(^7\) (Figure 8). In addition, we also assessed time to 50\% ST-segment resolution.

![Figure 8](image)

**Figure 8** ST-VM trend-curve of a patient with ST-elevation myocardial infarction.

**Follow-up and Endpoints**

The outcome events in the substudies of the ASSENT-2 and ASSENT-PLUS trials were all-cause mortality and re-infarction at 30 days and mortality at one year in paper I and one-year mortality in paper II. Event rates at 30 days were collected at a follow up visit while the one-year mortality was evaluated by patient records and telephone contacts. Three patients were lost to follow up at one year (paper I). The definition of re-infarction during the initial 18 hours after start of thrombolysis was recurrent signs and symptoms of ischemia accompanied by new or repeated ST-elevation of \(\geq 0.1\) mV in at least two contiguous leads lasting at least 30 minutes. After 18 hours, re-
Infarction was defined by the presence of new Q waves or new LBBB or (re)elevation of CK-MB to above the upper limit of normal and increased by ≥25% over the previously elevated level.

One-year mortality data in paper III and IV were obtained by merging the RIKS-HIA database with the National Cause of Death Register, which includes the vital status of all Swedish citizens. Complete follow-up in paper III was available until December 31, 2004.

Statistical methods

All statistics were calculated with SPSS software (version 11 and 12, Statistical Package for the Social Sciences). Baseline characteristics were summarized as medians (with 25th-75th percentile) or percentages in all papers. In all statistical analyses, a p-value of less than 0.05 was considered significant.

Paper I and II: Differences between categorical baseline variables were evaluated with the chi-square test (for trend in paper II). The Mann-Whitney U test or the Kruskal-Wallis test were used to compare continuous variables. Correlations were assessed by the Spearman’s rank statistics. To compare the predictive capacity of NT-proBNP, tnt and time to 50% ST-resolution in paper II, receiver operating characteristic (ROC) was used. Kaplan-Meier curves were constructed to illustrate the risk for death during the one year of follow-up and the log-rank test was done to compare the risk between strata in paper II. Independent predictors of one-year mortality were identified with stepwise multivariable logistic regression analyses (NT-proBNP was log-transformed due to its skewed distribution). Variables with a p-value of less than 0.05 were entered in the model and variables with a value of more than 0.1 were removed. The independent predictors of one-year mortality as well as tnt (paper I) and Killip class (paper II) were then evaluated in multivariable logistic regression models. Additional logistic regression analyses were performed to adjust for study (ASSENT-2 or ASSENT-PLUS) and to test for the interaction between ST-resolution and NT-proBNP and tnt.

A clinical risk index, previously described by Morrow et al.116 (heart rate x(age/10)²)/systolic blood pressure) was calculated for each patient for evaluation of its interaction with tnt and ST-resolution at 60 minutes. According to Morrow et al.116, this risk index was used to dichotomise patients into a low-risk group (Morrow-index ≤22.5) and a high-risk group (Morrow-index >22.5).

Paper III and IV: Differences between categorical variables were evaluated with the chi-square test and between continuous variables by the Mann-Whitney U-test. Kaplan-Meier curves were constructed to illustrate the risk for death during the one year of follow-up.

In paper III the relation between the two patient strata and one-year mortality was evaluated in two models of multiple logistic regression analyses.
Model 1 included rescue angioplasty and variables listed in paper III. In model 2, only patients who survived the first 14 days were included and revascularisation within 14 days was added to the model.

In paper IV the relations between the three patient strata (ASSENT-2, non-A2 and non-A2-Hosp) and one-year mortality were evaluated in three different models of multiple logistic regression analyses. Included variables are listed in paper IV. Model 1a compared the odds of death for the non-A2 with the odds of death for the ASSENT-2 patients. Model 2 compared non-A2-Hosp with ASSENT-2 and finally, model 3 included non-A2 versus non-A2-Hosp. Another multiple logistic regression model including the same covariates (as in model 1a) was performed to evaluate enrolment in the ASSENT-2 trial (yes/no).

Interaction analyses were performed between gender and treatment strategy (paper III) and gender and trial participation or not (paper IV) and one-year mortality using multiple logistic regression analyses.
RESULTS

Early risk stratification in STEMI (paper I and II)
Clinical characteristics at baseline and mortality rates in the ASSENT-2, ASSENT-PLUS and study I are shown in Table 1. The short- and long-term mortalities were lower in study I and the subgroup of patients in study II with information on ST-resolution (n=456) (Figure 5) compared to the entire ASSENT-2 trial, despite a higher median age in our substudy.

Table 1 Baseline Characteristics and Clinical Outcomes in the Assent-2, Assent-plus and substudy I.

<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>Assent-2 (n=16949)</th>
<th>Assent-plus (n=434)</th>
<th>Substudy* (n=516)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 (52-70)</td>
<td>64 (56-74)</td>
<td>68 (58-75)</td>
</tr>
<tr>
<td>Male gender</td>
<td>76.9</td>
<td>70.5</td>
<td>71.5</td>
</tr>
<tr>
<td>Time to therapy (min.)\†</td>
<td>162 (114-228)</td>
<td>140 (95-205)</td>
<td>150 (100-215)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>16.1</td>
<td>12.0</td>
<td>12.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>38.2</td>
<td>32.0</td>
<td>30.2</td>
</tr>
<tr>
<td>Previous MI</td>
<td>15.8</td>
<td>14.5</td>
<td>15.9</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>39.8</td>
<td>44</td>
<td>42.3</td>
</tr>
<tr>
<td>SBP (mmHg)\†</td>
<td>133 (120-150)</td>
<td>140 (122-155)</td>
<td>140 (127-156)</td>
</tr>
<tr>
<td>Heart rate (bpm)\†</td>
<td>72 (62-85)</td>
<td>70 (60-80)</td>
<td>70 (60-80)</td>
</tr>
<tr>
<td>Killip class&gt;1</td>
<td>12.9</td>
<td>12.0</td>
<td>11.9</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>6.2</td>
<td>4.6</td>
<td>3.7</td>
</tr>
<tr>
<td>One-year mortality</td>
<td>9.6</td>
<td>7.1</td>
<td>6.0</td>
</tr>
<tr>
<td>Re-infarction by 30 days</td>
<td>4.0</td>
<td>6.4</td>
<td>4.7</td>
</tr>
</tbody>
</table>

MI=myocardial infarction; SBP=systolic blood pressure.
\*386 patients from Assent-2 and 130 patients from Assent-plus; \†median (25th-75th percentile)

Markers of myocardial damage (paper I)
Half of the patients (n=257) had no detectable tnT level on admission and the others (n=259) had a median level of 0.08 μg/L (25th-75th percentile, 0.03-0.23 μg/L). The majority of patients (n=400, 77.5%) were tnT negative (<0.1 μg/L), and less than one fourth were tnT positive (≥0.1 μg/L) on admission. Patients with elevated tnT were older, had higher probability of anterior infarction, higher heart rate and longer time from symptom onset to therapy than those without elevation. Patients without tnT elevation had a
lower 30-day and one-year mortality compared to those with elevated tnT, whereas there was no difference in the rate of re-infarctions according to tnT level (Figure 9). There was a moderate positive correlation between tnT levels and duration of symptoms ($r=0.32$, $p<0.001$). However, there was no statistically significant difference in one-year mortality between patients with tnT elevation with symptom duration <2 (9.5%), 2-4 (14.6%) and 4-6 hours (13.0%) ($p=0.85$).

**ST-segment resolution at 60 minutes (paper I)**

Median time to 50% ST-segment resolution was 76 minutes (25th-75th percentile, 41-146 minutes), and at 60 minutes, less than half showed ≥50% ST-resolution ($n=215$, 41.7%) and consequently the majority no ST-resolution ($n=301$, 58.3%). Patients without ST-resolution had longer time from symptom onset to therapy and higher probability of previous myocardial infarction compared to the others. Patients with ST-resolution at 60 minutes had a lower 30-day and one-year mortality than those without, while there was no difference in the rate of re-infarctions according to ST-resolution (Figure 9).
Markers of myocardial dysfunction (paper II)

During one year follow-up 66 (8.4%) deaths occurred in the whole study population (Figure 5). More than half of the study population (n=443) had normal levels of NT-proBNP on admission according to age and gender (≤/>65 years, ≤184/≤269 ng/L in men, ≤/>65 years, ≤268/≤391 ng/L in women). The remaining patients had a median level of 742 ng/L (395-1894). Patients were divided in relation to 1) normal, 2) above normal, but below median (intermediate) (n=169) and 3) above the median (high) (n=170) level of NT-proBNP. There was a stepwise increase in age, heart rate, Killip class, the rate of previous MI and time from symptom onset to therapy in relation to higher levels of NT-proBNP. However, the correlation between NT-proBNP and symptom duration was weak (r=0.17, p<0.001). The distribution of NT-proBNP levels and baseline characteristics according to NT-proBNP were similar in the subgroup of patients with ST-monitoring.

There was a stepwise increase in one-year mortality according to increasing levels of NT-proBNP (3.4%, 6.5% and 23.5%, respectively) (Figure 10). Accordingly, there was a striking mortality difference between patients with high and those with normal level of NT-proBNP (O.R. 8.8; 4.7-16.4, p<0.001). There was also significantly higher mortality in those with high compared to intermediate level of NT-proBNP (O.R. 4.4; 2.2-9.0, p<0.001). A high NT-proBNP level (>742 ng/L) yielded a sensitivity and specificity in the whole study population of 61% and 82%, respectively. The corresponding positive and negative predictive values were 24% and 96%, respectively.

![Figure 10](image-url) Cumulative probability of death during one year according to the level of NT-proBNP (n=782).
Prognostic interactions of NT-proBNP, tnT and ST-resolution (paper I and II)

There were weak positive correlations between time to 50% ST-resolution and both tnT and NT-proBNP levels, (r=0.12, p=0.008, (n=516)) and (r=0.13, p=0.005, (n=456)), respectively. In contrast, the correlation between levels of tnT and NT-proBNP was moderate (r=0.43, p<0.001, (n=782)).

Figure 11 illustrates the univariable association between levels of NT-proBNP, tnT and time to 50% ST-resolution and one-year mortality by ROC-curves. Notably, the areas under the curves (AUC) showed a strong trend for NT-proBNP to be more strongly associated with mortality than the other variables (NT-proBNP versus tnT, p=0.056 and NT-proBNP versus time to 50% ST-resolution, p=0.052, respectively). Moreover, when evaluated in the whole study population in paper II the AUC for NT-proBNP (0.79) and tnT (0.71) were unaltered and NT-proBNP was significantly more strongly related to mortality than tnT (p=0.026). The AUC for NT-proBNP (0.76, n=574) was similar for patients without previous MI and in Killip class I on admission.

**Figure 11** Receiver operator characteristic curve concerning death at one year for NT-proBNP, Troponin T and time to 50% ST-segment resolution with an area under the curve (95% confidence interval) of 0.81 (0.72-0.90), 0.67 (0.56-0.79) and 0.66 (0.56-0.77), respectively (n=456).
When ST-resolution at 60 minutes and tnT was tested in a multivariable logistic regression analysis (paper I), no ST-resolution was and elevated tnT (O.R. 1.95; 0.84-4.51) tended to be, independently related to one year mortality (Table 2).

In a multivariable analysis including all patients with information on NT-proBNP (n=782) and thus not including information on early ST-resolution in the model; age, heart rate, systolic blood pressure (SBP), “elevated” tnT and log(NT-proBNP) were independently associated with one-year mortality (Table 3, model 1). In a restricted version of model 1 that only included patients with data on ST-resolution (n=456), NT-proBNP but not tnT (O.R. 1.52; 0.60-3.85) contributed independently. When 50% ST-resolution at 60 minutes was added to the model, both log(NT-proBNP) and <50% ST-resolution were independently associated with mortality in contrast to tnT (Table 3, model 2).

| Table 2 Multivariable analysis for one-year mortality (n=513) (paper I). |
|-----------------------------|---------------------|---------------------|
|                            | Multivariable OR (95% CI) | p-value            |
| Age (years)                | 1.13 (1.10-1.17) | <0.001             |
| Heart rate (bpm)           | 1.04 (1.03-1.05) | 0.001              |
| SBP (mmHg)                 | 0.97 (0.97-0.99) | 0.005              |
| ST-res <50% at 60 min.     | 3.53 (1.31-9.38) | 0.012              |
| tnT ≥0.1 µg/L              | 1.95 (0.84-4.51) | 0.12               |

SBP=systolic blood pressure; ST-res=ST-segment resolution.

| Table 3 Univariable and multivariable logistic regression analysis for one-year mortality. |
|-------------------------------------|---------------------|---------------------|
| Univariable Model 1 (n=782)       | Multivariable Model 2 (n=456)  |
| Multivariable Model 2 with interaction OR (95% CI) |
| Age (years) | 1.13 (1.10-1.17) | 1.11 (1.06-1.15) | 1.08 (1.02-1.14) | 1.09 (1.03-1.15) |
| Heart rate (b.p.m.) | 1.04 (1.03-1.05) | 1.02 (1.01-1.04) | 1.02 (1.01-1.05) | 1.03 (1.01-1.05) |
| SBP (mmHg) | 0.98 (0.97-0.99) | 0.98 (0.96-0.99) | 0.98 (0.96-0.99) | 0.98 (0.96-0.99) |
| Killip class >1 | 3.28 (1.86-5.76) | 1.74 (0.89-3.40) | 1.11 (0.38-3.26) | 1.09 (0.37-3.20) |
| Log(NT-proBNP)* | 3.04 (2.33-3.97) | 1.69 (1.20-2.37) | 2.27 (1.33-3.87) |
| ST-resolution <50%‡ | NA | NA | 2.97 (1.58-5.59) |
| ST-resolution ≥50%‡ | NA | NA | 1.15 (0.50-2.63) |
| ST-resolution <50%† | 3.02 (1.20-7.56) | NA | 3.06 (1.07-8.76) | 1.42 (0.41-4.90) |
| Troponin T ≥0.1 (µg/L) | 4.56 (2.72-7.65) | 2.25 (1.21-4.19) | 1.35 (0.52-3.48) | 1.30 (0.49-3.50) |

M2= Model 2; SBP=systolic blood pressure; NA=not applicable

*Log(NT-proBNP) standardised to have mean=0 and SD=1; ‡at 60 minutes; †OR for patient with mean log(NT-proBNP) representing a value of NT-proBNP of 256
Combinations of NT-proBNP, tnT and ST-resolution (paper I and II)

When combining the risk markers, an even better risk stratification was achieved. Figure 12a illustrates the marked difference in one-year mortality between the group with tnT elevation and without ST-resolution and the group with no tnT elevation and with ST-resolution (O.R. 6.4; 2.4-17.2, p<0.001. Patients were also stratified according to a combination of our tnT and ST-resolution indices with Morrows’ clinical risk index\textsuperscript{116} (paper I). Patients with a Morrow-index >22.5 and tnT elevation and without ST-resolution compared to those with a Morrow-index \leq 22.5 and the other combinations of tnT and ST-resolution had a one-year mortality of 25.0% versus 2.3% (O.R. 14.3; 4.8-42.3, p<0.001).

There was a gradual increase in mortality according to increasing levels of NT-proBNP in both patients with and without tnT elevation (Figure 12b). There was a profound difference in mortality between the group with high NT-proBNP and without ST-resolution and the group with normal NT-proBNP and with ST-resolution (O.R. 20.5; 4.6-92.4, p<0.001) (Figure 12c). Notably, the difference in mortality between patients with and without ST-resolution was mainly restricted to those with high levels of NT-proBNP. Accordingly, there was a significant interaction between NT-proBNP and 50% ST-resolution at 60 minutes (p=0.04) (Table 3).

Figure 12a One-year mortality according to the combination of Troponin T (\(\mu\)g/L) and ST-segment resolution (%) at 60 minutes (n=513).
**Figure 12b** One year mortality according to the combination of NT-proBNP (ng/L) and tnT (µg/L) (n=782).

*Figure 12c* One year mortality according to the combination of NT-proBNP (ng/L) and ST-segment resolution (%) at 60 min (n=456).
Prehospital and in-hospital thrombolysis (paper III)

General findings and time delays

There were large variations in the proportion of prehospital treated patients at different hospitals (median 22.6%, 10th-90th percentile, 1.5%-51.6%) reflecting different treatment traditions (Figure 13). Also, a decrease in the use of in-hospital thrombolysis (2001 (n=1249), 2004 (n=523)) was observed during the registration period due to a marked increase in primary PCI, while the rate of PHT remained stable (2001 n=391, 2004 (n=396)).

The PHT patients compared with the in-hospital treated were 3 years younger (in median), less often female (26.9% versus 31.2%), less likely to have previous cardiac disease and co morbid conditions and had fewer medications indicative of ischemic heart disease and heart failure. In a multivariable analysis 7 variables at baseline including female gender were independently associated with a lower probability to receive PHT (Figure 14).

The median time from symptom onset to treatment was 110 minutes in the PHT group and 162 minutes in the in-hospital group and PHT thus reduced the median time to thrombolysis with 52 minutes (Table 4). Women showed longer median symptom durations than men, especially among in-hospital but also among PHT treated patients, 185 vs. 155 minutes and 120 vs. 108 minutes, respectively. In an analysis restricted to patients with information on time of ambulance arrival on scene, there was no statistical difference between the two regimens in time from symptom onset to ambulance arrival.

![Figure 13 Distribution of prehospital and in-hospital thrombolysis at 75 hospitals.](image)
Figure 14 Factors influencing the probability to receive prehospital thrombolysis (significant in multivariable analysis).
*night time after 18.00 to 08.00 and weekends; †10 years increment

Table 4 Time delays (minutes) (median (25th-75th percentile)).

<table>
<thead>
<tr>
<th></th>
<th>Prehospital lysis (n=1911)</th>
<th>In-hospital lysis (n=4328)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset to treatment</td>
<td>110 (68-195)</td>
<td>162 (105-275)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergency department to treatment*</td>
<td>-</td>
<td>40 (25-70)</td>
<td>-</td>
</tr>
<tr>
<td>Coronary care unit to treatment†</td>
<td>-</td>
<td>21 (12-40)</td>
<td>-</td>
</tr>
<tr>
<td>Symptom to ambulance arrival‡</td>
<td>78 (39-155)</td>
<td>77 (36-160)</td>
<td>0.78</td>
</tr>
<tr>
<td>Ambulance arrival to prehos ECG§</td>
<td>15 (9-22)</td>
<td>16 (10-24)</td>
<td>0.10</td>
</tr>
<tr>
<td>Prehos ECG to treatment‡</td>
<td>16 (10-25)</td>
<td>52 (36-80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ambulance arrival to treatment‡</td>
<td>31 (23-41)</td>
<td>70 (52-99)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Only patients with information on time from symptom onset to treatment.
*assessed in 3073; †assessed in 1245 (in those without time from emergency department to treatment); ‡assessed in 819/1597; §assessed in 752/801; *assessed in 1082/1075

Treatment, complications and procedures
About 28% of the in-hospital treated patients received Streptokinase as thrombolytic agent in contrast to none of the PHT patients (Table 5). There were fewer complications at the CCU indicative of congestive heart failure in PHT than in-hospital treated patients, whereas there was no statistical difference in cerebral bleedings. Multiple logistic regression analyses revealed PHT to be strongly associated with lower odds of development of
heart failure at the CCU (OR 0.69; 0.59-0.80, p<0.001) and cardiogenic shock on admission (OR 0.61; 0.48-0.76, p<0.001).

Information on LVEF was available in 58% and 50% of the PHT and in-hospital treated hospital survivors. Compared with in-hospital treated, LVEF was higher in the PHT group (Table 5). Also, when evaluated in patients without previous MI and previous CHF, LVEF showed a similar distribution according to treatment groups. There was a stepwise increase in one-year mortality according to decreasing LVEF in patients without previous MI and CHF, 1.7%, 2.2%, 7.7% and 16.3%. Invasive procedures were more frequently performed and the use of guideline-recommended medications at discharge was somewhat more common in PHT patients.

Table 5 In-hospital treatment, complications, procedures and discharge medication.

<table>
<thead>
<tr>
<th>(%)</th>
<th>Prehospital lysis (n=1690)</th>
<th>In-hospital lysis (n=3685)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptokinase</td>
<td>0</td>
<td>27.8</td>
<td>-</td>
</tr>
<tr>
<td>Intravenous beta-blocker</td>
<td>63.6</td>
<td>58.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intravenous diuretics</td>
<td>19.6</td>
<td>29.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip class &gt;1</td>
<td>14.9</td>
<td>21.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPAP therapy</td>
<td>1.4</td>
<td>4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiogenic shock on admission</td>
<td>6.8</td>
<td>11.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPR (ventricular fibrillation)</td>
<td>2.3</td>
<td>4.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Reinfarction within hospital stay</td>
<td>3.1</td>
<td>3.4</td>
<td>0.51</td>
</tr>
<tr>
<td>Cerebral bleeding</td>
<td>1.4</td>
<td>0.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Echocardiography*</td>
<td>71.0</td>
<td>70.5</td>
<td>0.73</td>
</tr>
<tr>
<td>LVEF* † &gt;50%</td>
<td>49.6</td>
<td>42.4</td>
<td></td>
</tr>
<tr>
<td>41-50%</td>
<td>31.1</td>
<td>33.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>31-40%</td>
<td>16.4</td>
<td>17.5</td>
<td></td>
</tr>
<tr>
<td>&lt;30%</td>
<td>2.8</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Rescue PCI</td>
<td>20.4</td>
<td>13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Revasc. within 14 days‡</td>
<td>45.9</td>
<td>36.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discharge medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>89.3</td>
<td>88.9</td>
<td>0.66</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>6.4</td>
<td>6.7</td>
<td>0.64</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>92.7</td>
<td>89.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>75.5</td>
<td>72.1</td>
<td>0.01</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>51.9</td>
<td>53.5</td>
<td>0.29</td>
</tr>
<tr>
<td>Diuretics</td>
<td>18.6</td>
<td>27.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CPAP=continuous positive airway pressure; LVEF=left ventricular ejection fraction; PCI=percutaneous coronary intervention; revasc.=revascularisation
†hospital survivors; †assessed in 931/1725; ‡14-days survivors

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Outcome

Most of the mortality difference occurred during the first month of follow-up (Figure 15). At 30 days the crude mortality in the whole study population was 5.4% vs. 8.3% (p<0.001) in the PHT and in-hospital treated group, respectively. However, the curves continued to separate after 30 days of follow-up, but to a lesser degree and at one year the crude mortality was 7.2% vs. 11.8% (p<0.001) (OR 0.57; 0.46-0.73) in PHT and in-hospital treated patients, respectively. The cause of death at one year were equally distributed in PHT and in-hospital treated with respect to cardiovascular mortality (84.2% versus 86.7%, p=0.63), respectively.

When stratified according to time to treatment, a stepwise increase in one-year mortality was observed among in-hospital treated patients and partly among PHT (not the first two hours) patients, 0-1 hour; 6.5% and 8.5%, 1-2 h; 9.4% and 5.1%, 2-3 h; 11.5% and 5.3%, 3-4 h; 12.2% and 7.1%, 4-5 h; 12.9% and 9.7%, 5-6 h; 17.9% and 8.9%, >6 h; 15.4% and 12.9%, respectively.

In a multiple logistic regression analysis adjusting for a large number of risk factors at baseline and rescue angioplasty, PHT compared with in-hospital treatment was associated with lower one-year mortality (OR 0.71; 0.55-0.91, p=0.007) (Figure 16). This lower adjusted one-year mortality was still present when the analysis was restricted to patients without streptokinase therapy treated within 6 hours of symptom onset (OR 0.69; 0.51-0.94,
p=0.02). Also, when evaluating patients that survived the first 14 days and
adjustment for revascularisation within 14 days was done, PHT was associ-
ated with a lower adjusted one-year mortality (OR 0.61; 0.41-0.93, p=0.02).

With respect to sex, there was no statistically significant difference in
one-year mortality (and no differences in causes of death) for women ac-
cording to PHT or in-hospital thrombolysis (10.4% versus 12.7%, p=0.25).
Accordingly, there was a significant interaction between gender and treat-
ment strategy (p=0.02). Thus, the benefit of PHT versus in-hospital throm-
bolysis was restricted to men (OR 0.57; 0.42-0.78) whereas no gain was
observed in women (OR 1.05; 0.68-1.61) after controlling for other risk fac-
tors.

![Figure 16 Factors influencing one-year mortality (significant in multivariable analy-
sis).](chart)

*10 years increment

**Trial and non-trial patients (paper IV).**

Baseline characteristics, treatment, complications and procedures

Table 6 shows baseline characteristics of ASSENT-2 and non-A2 patients.
The ASSENT-2 compared to the non-A2 patients were younger, less often
female, had lower prevalence of co morbid conditions and had lesser medica-
tions indicative of coronary heart disease and heart failure. As expected,
contraindications for inclusion in the ASSENT-2-trial (previous stroke, car-
diopulmonary resuscitation (CPR) before admission and oral anticoagulants)
were more common among the non-A2 patients. In a multivariate analysis,
including patients at ASSENT-2 recruiting hospitals, 8 variables at baseline were independently associated with no trial enrolment (Figure 17).

About two thirds of the non-A2 patients received Streptokinase as thrombolytic agent in contrast to the ASSENT-2 patients who all received a tPA-agent (Table 7). There were fewer complications during hospital stay such as congestive heart failure, hypotension and CPR in ASSENT-2 than in non-A2 patients while there was no difference in thrombolysis complications or revascularisation within 14 days. The use of guideline-recommended medications at discharge was similar, only beta-blockers were more common among ASSENT-2 patients.

Table 6 Baseline characteristics according to trial participation or not at ASSENT-2 recruiting hospitals.

<table>
<thead>
<tr>
<th></th>
<th>Assent-2 (n=729)</th>
<th>non-A2 A2 recruiting hospitals (n=2048)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>67 (58-74)</td>
<td>70 (60-78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>30.5</td>
<td>34.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Risk factors/history of disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12.6</td>
<td>17.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25.8</td>
<td>27.2</td>
<td>0.47</td>
</tr>
<tr>
<td>LBBB</td>
<td>2.3</td>
<td>5.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6.3</td>
<td>7.4</td>
<td>0.32</td>
</tr>
<tr>
<td>Previous MI</td>
<td>11.0</td>
<td>16.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous PCI/CABG</td>
<td>4.3</td>
<td>4.4</td>
<td>0.90</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>2.7</td>
<td>8.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous heart failure</td>
<td>12.1</td>
<td>18.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment on admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>17.7</td>
<td>26.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>0.3</td>
<td>1.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>23.6</td>
<td>25.6</td>
<td>0.29</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>8.1</td>
<td>8.9</td>
<td>0.51</td>
</tr>
<tr>
<td>Diuretics</td>
<td>11.7</td>
<td>18.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digitalis</td>
<td>2.5</td>
<td>4.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Statins</td>
<td>5.8</td>
<td>5.8</td>
<td>1.0</td>
</tr>
<tr>
<td>CPR before admission</td>
<td>0.3</td>
<td>1.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to therapy (hours)*</td>
<td>2.8 (1.8-4.2)</td>
<td>3.3 (1.9-6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission on-call time†</td>
<td>50.9</td>
<td>64.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; LBBB=left bundle branch block; CPR=cardiopulmonary resuscitation
*median (25th-75th percentile); †night time after 18.00 to 08.00 and weekends
Outcome

The Kaplan-Meier curves for trial versus non-trial patients diverged early and most of the mortality difference occurred during the first month of follow-up (Figure 18). Thus, at 30 days the mortality was 5.8% versus 15.1% and 14.4% in the ASSENT-2, non-A2 and non-A2-Hosp groups of patients (p<0.001 for both). At one-year, the mortality was still more than twice as high among both non-A2 and non-A2-Hosp patients compared with the ASSENT-2 patients (20.3% and 19.0% versus 8.8%, p<0.001 for both).

In a multiple logistic regression analysis, adjusting for a large number of risk factors at baseline as well as heart failure at the CCU, belonging to the non-A2 group was still independently associated with a higher one-year mortality compared to the ASSENT-2 group, (O.R. 1.99; 1.45-2.73, p<0.001) (Figure 19). When restricting the analysis to patients with tPA therapy treated within 6 hours and without previous stroke, oral anticoagulants and CPR before admission (model 1b), the higher mortality among the non-A2 patients was even more pronounced (O.R. for non-A2 versus ASSENT-2, 3.28; 1.98-5.41, p<0.001) (Table 8). After the same adjustments, a similar increase in one-year mortality was found among non-A2-Hosp compared to ASSENT-2 patients. When evaluating one-year mortality for pa-
tients who survived the first two days, there was still a higher mortality, but less prominent, among non-trial patients (Table 8).

With respect to gender, the one-year mortality for women in the non-A2 group versus women in the trial was 26.3% versus 9.6% and for men 17.0% versus 8.4%, respectively. In multivariable analyses, the one-year mortality difference for non-A2 versus ASSENT-2 women (O.R. 2.56; 1.45-4.51, p=0.001) was more pronounced compared to non-A2 versus ASSENT-2 men (O.R. 1.61; 1.1-2.37, p=0.014), although there was no significant interaction between female gender and trial participation or not and mortality (p=0.12).

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Treatment, complications, procedures and discharge medication according to trial participation or not at ASSENT-2 recruiting hospitals.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aggregate A2 recruiting hospitals (n=729)</td>
</tr>
<tr>
<td></td>
<td>non-A2 recruiting hospitals (n=2048)</td>
</tr>
<tr>
<td></td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>Catheterisation lab. in-house</td>
<td>35.1</td>
</tr>
<tr>
<td>Treatment</td>
<td>tPA-agent/Streptokinase</td>
</tr>
<tr>
<td></td>
<td>Intravenous beta-blocker</td>
</tr>
<tr>
<td>Complications</td>
<td>Congestive heart failure*</td>
</tr>
<tr>
<td></td>
<td>CPAP therapy</td>
</tr>
<tr>
<td></td>
<td>Hypotension†</td>
</tr>
<tr>
<td></td>
<td>CPR</td>
</tr>
<tr>
<td></td>
<td>Reinfarction</td>
</tr>
<tr>
<td></td>
<td>Thrombolysis complication‡</td>
</tr>
<tr>
<td>Procedures</td>
<td>Echocardiography</td>
</tr>
<tr>
<td></td>
<td>Rescue PCI</td>
</tr>
<tr>
<td></td>
<td>Revascularisation within 14 day</td>
</tr>
<tr>
<td>Discharge medication§</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Oral anticoagulants</td>
</tr>
<tr>
<td></td>
<td>Beta-blockers</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
</tr>
</tbody>
</table>

Lab=labatory; tPA=tissue plasminogen activator; CPAP=continuous positive airway pressure *presence of pulmonary rales and/or administration of intravenous diuretics; †systolic blood pressure <90 mmHg for ≥1 hour; ‡intracranial or severe bleeding; §in hospital survivors
Figure 18 Kaplan-Meier curves showing the cumulative probability of death during the follow-up period of one year for the three patient strata, ASSENT-2, non-A2 and non-A2-hosp.

Figure 19 Factors influencing one-year mortality at ASSENT-2 recruiting hospitals (significant in multivariate analysis).

*10 years increment; †presence of pulmonary rales and/or administration of intravenous diuretics
Table 8  Multiple logistic regression analysis for one-year mortality and between day 3 to 365.

<table>
<thead>
<tr>
<th>Model</th>
<th>1-year mortality</th>
<th>Mort. day 3-365</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% C.I.)</td>
<td>p-value</td>
</tr>
<tr>
<td>Model 1a (n=2777)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-A2 vs. Assent-2</td>
<td>1.99 (1.45-2.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 1b* (n=980)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-A2 vs. Assent-2</td>
<td>3.28 (1.98-5.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2 (n=1693)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-A2-Hosp vs. Assent-2</td>
<td>1.88 (1.31-2.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 3 (n=3012)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-A2 vs. non-A2-Hosp</td>
<td>1.04 (0.82-1.30)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Model 1a, 2 and 3 included 20 covariates (see “Methods” section of text); OR=odds ratio; CI=confidence interval; *Only patients with tPA therapy treated within 6 hours and without previous stroke, oral anticoagulants and CPR before admission were included.
DISCUSSION

Outcome in relation to tnT, ST-segment resolution and NT-proBNP (paper I and II)

Elevated tnT on admission was associated with a 3 - 4 times higher short- and long-term mortality in STEMI patients treated with fibrinolytics as in previous studies\textsuperscript{39-41}. After adjustments for risk factors at baseline and ST-resolution the Odds Ratio of around 2 for elevated tnT in relation to mortality was similar in our study and in the large Gusto III substudy\textsuperscript{41}. The fact that elevated tnT was not an independent predictor of mortality in our study is probably explained by a relatively small sample size and few events and also that our multivariable model included information on early ST-resolution in contrast to the Gusto III study. We found a moderate positive correlation between symptom duration and tnT level in accordance with previous studies\textsuperscript{41}. However, among the relatively few patients with tnT elevation in our study there was no significant difference in mortality in relation to short and long symptom duration, which also was found in the Gusto-III substudy\textsuperscript{41}. Explanations for this might be that patients with tnT elevation and short symptom duration may have had episodes of ischemia with release of tnT before onset of symptoms of the actual infarct and different thresholds of pain perception as suggested by Ohman et al.\textsuperscript{41}. Thus, in the former cases the index infarct might be an early re-infarction which has been shown to be associated with adverse outcome\textsuperscript{117}. Interestingly, this hypothesis accords with a recently reported finding that in at least 50% of cases with STEMI, the occlusive coronary thrombi were days or weeks old which indicates a long period of plaque instability and thrombus formation before coronary occlusion in many STEMI patients\textsuperscript{118}. Patients without tnT elevation and long symptom duration on the other hand may have had ischemic preconditioning\textsuperscript{33} and/or collateral circulation\textsuperscript{32} resulting in less or no tnT release. Hence, it might be speculated that admission tnT is a more accurate marker of ischemic time than symptom duration.

ST-segment resolution at 60 minutes was independently associated with short- and long-term mortality also when adjusting for tnT, as in previous studies evaluating ST-resolution at a later time point but without information on tnT\textsuperscript{70,71}.

Admission NT-proBNP was a strong independent predictor of long-term mortality in STEMI consistent with previous evaluations of NT-proBNP.
(and BNP) and short term mortality. For the first time NT-proBNP was evaluated together with ST-resolution, tnT and other well known risk factors, and still independently predicted mortality. As in a previous trial, NT-proBNP were equally predictive in patients without previous MI and signs of heart failure on admission. Accordingly, Killip class provided no independent prognostic information when NT-proBNP was added to the multivariable model (Table 3).

We found only a weak correlation between symptom duration and NT-proBNP, which was somewhat unexpected considering the time dependent rise of BNP in the early phase after STEMI. One explanation for this might be that a patient’s recollection of the symptom duration is highly subjective. Thus, admission tnT, which is believed to be a more objective marker of ischemic time as discussed above, had a stronger correlation to NT-proBNP.

Prognostic interactions and combinations between NT-proBNP and tnT and ST-resolution (paper I and II)

When testing NT-proBNP in multivariable analysis including well known predictors of outcome and tnT but not ST-resolution (model 1, Table 3), both NT-proBNP and tnT independently contributed to mortality prediction in contrast to previous studies. However, when model 1 was restricted to patients with data on ST-resolution, tnT no longer independently contributed, which probably is explained by the smaller sample size and fewer events in this subgroup of patients, as discussed above. Finally, when information on ST-resolution at 60 minutes was added, NT-proBNP and ST-resolution independently predicted mortality in contrast to tnT (model 2, Table 3). Thus, these results suggest that NT-proBNP and 50% ST-resolution at 60 minutes are complementary concerning their pathophysiological mechanisms in relation to mortality, which also was indicated by a weak correlation. Accordingly, there was a significant interaction between NT-proBNP and ST-resolution and the benefit of an early ST-resolution was mainly restricted to patients with high levels of NT-proBNP (Table 3 and Figure 12c). In contrast, NT-proBNP and tnT seemed to have more similar mechanisms in relation to mortality as indicated by a moderate correlation. The fact that NT-proBNP has been shown to be an indicator of myocardial ischemia per se and tnT of myocardial necrosis, might to some extent explain why NT-proBNP has greater prognostic accuracy on admission in STEMI than tnT, as discussed by Galvani et al., but also why they in part seem to be markers of similar pathophysiology in the early phase of STEMI. Another explanation for the stronger prognostic value of NT-proBNP compared to tnT could be that NT-proBNP integrates both previous and acute
cardiac dysfunction. However, the knowledge of tnt level in addition to NT-proBNP provided further risk stratification on admission (Figure 12b) especially before information on ST-resolution at 60 minutes was obtained.

The combination of NT-proBNP and early ST-resolution improved risk prediction. Hence, one third of the high risk patients with high NT-proBNP, who achieved early ST-resolution could be stratified into a moderate to low risk group, which might be explained by subsequent early tissue level reperfusion5. It might be hypothesized that patients with high levels of NT-proBNP on admission either have a large ongoing MI or a previously established left ventricular dysfunction with subsequent raised risk of adverse outcome, unless there is an early tissue level reperfusion. However, patients with normal admission NT-proBNP (more than half of the population) were at low risk almost regardless of 50% ST-resolution or not.

One limitation is that the population with ST-monitoring had a lower one-year mortality compared to the population with a plasma sample on admission, although baseline characteristics were similar (Figure 5). The mortality among the patients with a blood sample (tnt and/or NT-proBNP) was similar to the entire ASSENT-2 study population in contrast to the lower mortality in the patients with ST-monitoring. This lower mortality is in accordance with previous trials that evaluated ST-resolution30, 71 and is probably explained by the time criteria for ST-monitoring which excluded some of the patients with fatal early events. Also, patients with LBBB, a high risk group2, were prospectively excluded from ST-monitoring.

The influence on time delays with prehospital thrombolysis (paper III)

This study evaluates the use of prehospital and in-hospital thrombolysis in real life patients during the last 4 years from a nation wide perspective. The representativeness of the study population was strengthened by inclusion of all consecutive ambulance transported STEMI patients treated with thrombolytics from more than 90% of the hospitals within Sweden.

For the first time we could demonstrate that a prehospital versus in-hospital treatment strategy among ambulance transported real life patients was associated with a 52 minutes reduction in time to treatment which was in the range (0.5 to 1 hour) observed in randomised trials8, 13, 14. This was achieved in a system with only paramedics in the ambulances, but no physicians. Thus, a system with paramedics who transmit a prehospital ECG using telemedicine to a physician in the hospital for decision making and then administrating thrombolysis, seem as efficient in reducing treatment delay as a system with physician staffed ambulances13.
An in-hospital delay of 40 minutes represented approximately 75% of the time saved by PHT versus in-hospital treatment in real life patients, consistent with the GREAT study in which 67% of the time saved corresponded to in-hospital delay\textsuperscript{119}. An in-hospital treatment delay of 40 minutes compares well with a recent large US registry\textsuperscript{94}.

Prognostic value of prehospital thrombolysis (paperIII)

One problem in quantifying time dependent mortality benefit of thrombolytic therapy has been that patients with large infarcts and a worse prognosis tend to seek help earlier\textsuperscript{28, 119} and thus confounding mortality analyses of especially nonrandomised comparisons of prehospital and in-hospital thrombolysis\textsuperscript{28}. Our data appeared to be partly consistent with these previous findings, since there was a higher mortality among PHT patients that were treated during the first compared to the second hour from symptom onset. On the other hand, there was a stepwise increase in mortality according to longer symptom duration among in-hospital treated and PHT patients that was treated after the first hour. Also, it did not appear to be a selection bias with more early presenting patients that was treated with PHT, at least not in the subgroup with information on time from symptom onset to ambulance arrival (Table 4). Finally, the lower rates of complications at the CCU indicating severe heart failure in PHT treated compared with in-hospital treated patients as in a previous registry\textsuperscript{104}, but in contrast to another\textsuperscript{28}, seem also to some extent to contradict these previous observations. The fact that there were lower rates of complications at the CCU among PHT patients in our study might be explained by two factors. Firstly, it may in part reflect a selection bias with a reluctance to treat more critically ill patients with thrombolytics in the ambulance. This is supported by a lower incidence of co morbidity in the PHT group indicating a selection bias at presentation. Thus, LBBB and diabetes mellitus, shown to be associated with severe heart failure\textsuperscript{120, 121} were independently associated with a lower probability to receive PHT. Secondly, the earlier administration of reperfusion treatment may prevent the development of severe heart failure as in the randomised CAPTIM study\textsuperscript{83}. This is supported by a higher ejection fraction in the PHT group in patients without previous MI and heart failure indicating a larger amount of myocardial salvage. Also, this accords with the strong independent reverse association between PHT and admission cardiogenic shock and heart failure at the CCU after adjustments for baseline characteristics.

The Kaplan-Meier curves continued to separate after one month of follow-up resulting in 40% lower one-year mortality in the PHT group. This finding indicate an increasing benefit of PHT compared with in-hospital thrombolysis during one year of follow-up in accordance with the GREAT study\textsuperscript{119, 122}. One plausible explanation for this could be a higher extent of
myocardial salvage, shown to be highly dependent on time from symptom onset to thrombolysis. Accordingly, a higher LVEF was observed in the PHT group.

The fact that there were similar rates of cardiovascular mortality in both treatment groups indicated no excessive mortality from concomitant disease among in-hospital treated. With respect to safety, PHT appeared to be safe with no statistical difference in the rate of cerebral bleedings compared with in-hospital treated.

The time dependent mortality benefit of thrombolysis is exponential with most benefit if administered within 2 hours. Randomised PHT trials have shown that reducing time to treatment from 3.1 to 2.1 and 3.0 to 2.0 hours resulted in 21 and 69 lives saved per 1000 treated at 35 days and 30 months, respectively. The crude mortality benefit in the present study of PHT versus in-hospital thrombolysis was 29 and 46 lives saved per 1000 treated at 30 days and one year respectively, with a corresponding reduction in treatment delay of 52 minutes (2.7 to 1.8 hours). Thus, although not adjusted for differences at baseline and revascularisation, our crude results from real life patients support the findings in previous randomised trials and the magnitude of the mortality reduction in relation to the reduced treatment delay compares reasonable well. Furthermore, after adjustments for baseline risk factors and rescue angioplasty, PHT was independently associated with a lower mortality at one-year (Figure 16). Also, when adjusting for other potential confounders such as revascularisation within 14 days, and when excluding patients treated with streptokinase and with symptom duration more than 6 hours, PHT was still independently associated with a lower mortality. However, information on heart rate and systolic blood pressure at presentation, factors known to be strongly associated with mortality are not recorded in RIKS-HIA. It might be speculated that some of the excessive mortality rates among in-hospital treated could be explained by these factors, which we were unable to control for.

In the light of the encouraging observations regarding PHT in this registry, it was disappointing that women were less likely to receive PHT after controlling for other baseline characteristics. This supports previous findings that cardiovascular disease is treated less aggressive in women than in men although they have a worse prognosis. However, after controlling for co-morbidity including age, there was no benefit of PHT in women with respect to one-year mortality although a similar reduced time to therapy was observed in women as in men. Thrombolytic treatment has been shown to be equally effective for myocardial salvage regardless of gender. While absolute risk reduction in mortality with thrombolysis versus placebo has been similar according to gender, relative risk reduction was reported to be smaller for women since they have a higher absolute risk. Thus, the number of women treated with PHT in our study might not have been enough to detect a beneficial effect of the treatment. In addition, there was no indica-
tion that prehospital treatment among women resulted in excessive deaths from bleeding complications, since there were no differences in causes of death according to gender and treatment strategy.

In total 405 of 2095 (19.3%) with PHT and 396 of 4081 (9.7%) with in-hospital thrombolysis of the eligible patients had missing data regarding time to treatment and were excluded. However, patients with missing data had at large similar baseline characteristics as the included patients in relation to treatment modality, whereas 30-day mortality was higher (6.2%, PHT and 14.1%, in-hospital), especially among the excluded in-hospital treated. Thus, the mortality benefit for PHT was in fact even larger when these patients were included as well.

Selection of low risk patients into trials (paper IV)

Our study showed in accordance with previous trials that patients at lower age, male gender and with fewer risk factors for poor outcome were more likely to be included in trials of fibrinolytics. Several reasons for recruitment of low risk patients into clinical trials of fibrinolytics have been suggested. Firstly, exclusion criteria in trials are in general more restrictive than the ones used in clinical practice. For example, some of the exclusion criteria in the ASSENT-2 trial (previous stroke, CPR before admission and oral anticoagulants) were more common among non-A2 patients and the first two of them were independently related to no trial enrolment. Secondly, previous trials have suggested that physicians might be more reluctant to use fibrinolytic agents in older patients, given that the benefit appears to be lower and the risk of intracranial hemorrhage is greater, and thereby exclude them from trial participation. This is, however, not applicable to our study where the non-trial patients received fibrinolytics. Finally, it is more difficult and might take a longer time to obtain consent for trial participation from a seriously ill patient. This reason seemed to be one important explanation for the selection of lower risk patients in our study. Thus, non-A2 patients had more signs of early complications such as hypotension and CPR than the ASSENT-2 patients. Also, early signs of heart failure showed a strong trend to be independently related to no trial enrolment.

Interestingly, but not surprisingly, admission during on-call time was one of the strongest predictors of no trial enrolment. This might be explained by the limited time for, and experience of, recruiting patients into a clinical trial for the physician on call during nights and weekends.
Outcome in relation to trial and non-trial participation (paper IV)

The short- and long-term mortalities were similar for the cohort of ASSENT-2 patients in the present study compared with the ASSENT-2 trial and appears therefore representative regarding outcome for the whole ASSENT-2 trial.

As shown in Figure 19, belonging to the non-A2 population was next to higher age and heart failure the strongest predictor of long-term mortality in contrast to a small previous study. Moreover, when the comparison was restricted to ASSENT-2 eligible patients treated with tPA-agents within 6 hours of symptom onset, the adjusted outcome was even worse for the non-A2 patients. In addition, our results were not biased with non-trial patients not receiving thrombolytics, a group known to have a poorer outcome.

Another important finding was that patients with the strongest risk factors for mortality were the least likely to be enrolled in the trial. Thus, higher age, previous stroke, LBBB, diabetes and heart failure were all strongly associated with mortality and also independently associated with no trial enrolment.

Could differences in patient management explain this survival disadvantage? When evaluating treatments, procedures (including revascularisation) and discharge medications at the trial hospitals, there was no difference between non-A2 and ASSENT-2 patients except for a slightly higher use of beta-blockers among the latter. The greater use of tPA-agents in trial versus non-trial patients could not explain much of the mortality difference, which was in accordance with our multivariable evaluation.

Since we have adjusted for many of the known baseline risk characteristics in STEMI, explanations for the mortality difference between non-A2 and ASSENT-2 patients might be addressed by evaluating early complications at the CCU. Thus, heart failure, hypotension, continuous positive airway pressure therapy and CPR were more common in non-A2 patients, indicating more critically ill patients probably already on admission, and therefore possibly a lower probability to be included in the trial. Although we have adjusted for heart failure at the CCU, we had no information on admission Killip class, heart rate and systolic blood pressure, factors known to be strongly associated with outcome after STEMI. Hence, it might be expected that some of the excessive mortality in non-A2 patients could be explained by these factors, which we were unable to control for. In order to reduce the impact of early mortality from critically ill patients already on admission, an evaluation of mortality between day 3 and 365 was performed. As shown in Table 8, a higher mortality rate among non-trial patients was still present. However, the difference in mortality between day 3 and 365 was less pronounced, indicating that selection of less critically ill patients with a lower
early mortality into the trial, could explain at least a part of the one-year mortality difference.

One limitation is that 139 (14.8%) of the 939 ASSENT-2 patients in the ASSENT-2 database could not be identified in the RIKS-HIA database for unknown reasons. Possible explanations may be that they had wrong/missing information on date of admission, age, acute reperfusion treatment or another diagnosis and thereby not possible to include in our study or not recorded in RIKS-HIA registry. However, these “missing” patients compared with the ASSENT-2 patients who were identified had similar baseline characteristics and one-year mortality according to the ASSENT-2 database and would therefore not affect our results.

Clinical implications and future perspectives

Risk stratification

What risk markers should be recommended for early risk evaluation of patients with STEMI? Of clinical markers age, heart rate and SBP, constituting the risk index proposed by Morrow et al., were strong independent predictors of mortality as in previous trials. This risk index seems to be useful for risk prediction also when combined with nT and ST-resolution (paper I). Of the three variables that were especially evaluated in our studies, admission NT-proBNP seems to be the strongest predictor of mortality as indicated by the multivariable evaluations and when combined with ST-resolution at 60 minutes, available one hour later, risk assessment could be further modified. Identification of high risk patients with high NT-proBNP already on admission in STEMI may be helpful for selection of more intense interventional or pharmacological treatment strategies. Our study suggests that an early tissue level reperfusion, as indicated by an early ST-resolution, is especially important in patients with elevated NT-proBNP level and it could alter the adverse outcome for this high risk group. Thus, one might speculate that primary angioplasty could be valuable for these high risk patients, since tissue level reperfusion is achieved more frequently with primary angioplasty compared to thrombolysis. This and other new treatment strategies, according to high admission NT-proBNP levels, need to be tested in prospective trials. Admission NT-proBNP itself, or combined with admission nT, could also be a valuable tool for selecting high risk patients in future trials, testing new treatment strategies in STEMI.

By virtue of being a rapid and sensitive, but unspecific marker of reduced cardiac performance, NT-proBNP appears to be useful for selection of low risk patients. Thus, a normal NT-proBNP on admission (more than half of the study population) is associated with a very low mortality in accordance with an ACS study, almost regardless of ST-resolution and for the vast...
majority of these patients (>90%) with no tnt elevation. These patients seem to have a sufficient treatment and may be suitable for an early discharge.

**Prehospital diagnosis and thrombolysis**

The implementation of a prehospital diagnostic strategy and a possibility for PHT appear to be important in reducing time delays and mortality in STEMI with respect to PHT versus in-hospital thrombolysis. Importantly, a prehospital diagnostic strategy including prehospital ECG can be used to choose the most beneficial type of reperfusion method according to local settings. Time to reperfusion is important also in patients treated with primary PCI and although limited data exist in prehospital diagnosis and time delays with respect to primary PCI, a small study indicates a reasonable reduction in treatment delay with prehospital diagnosis. Thus, if the anticipated time to primary PCI (first balloon inflation) is less than 60 minutes compared with immediate thrombolysis as in a prehospital setting, primary PCI should be strongly considered. In addition, prehospital diagnosis in the setting of primary PCI, would also allow beneficial pretreatment with aspirin, clopidogrel and heparin. Nonetheless, in several countries such as Sweden, there are many settings with longer expected time than 60 minutes to primary PCI in which PHT should be preferred. Further studies are needed to elucidate the benefit of a prehospital diagnostic strategy in the setting of primary PCI.

It might be speculated that a further implementation of the use of prehospital ECG and prehospital thrombolysis and better education for the doctors on call about decision making on thrombolysis prehospitaly, are important to additionally reduce time delays and mortality in STEMI patients. Thus, more than 1000 patients in our study had a prehospital ECG but were nevertheless treated with thrombolysis in the hospital. Furthermore, patients admitted on-call time, were less likely to receive PHT, indicating that more unexperienced physicians on call were less likely to decide to start thrombolytic treatment in the ambulance. Another important issue is to obtain a higher proportion of patients with chest pain and suspected AMI to alert emergency services and subsequent ambulance transportation, which is mandatory for prehospital diagnosis. In our study 60% of the in-hospital treated patients used ambulance and in a recent US-registry only about 50% of patients with AMI used ambulance.

Our study revealed a continuous decrease in the use of in-hospital thrombolysis among ambulance transported patients during the study period, reflecting a similar increase in primary PCI, while the rate of PHT remained stable. In the future, a further decrease of in-hospital thrombolysis may be expected and warranted with respect to treatment delays and outcome. The optimal proportion of primary PCI and PHT is likely to differ between countries and regions according to geographic and logistic factors and the avail-
ability of primary PCI. A continuous evaluation of these two methods will be essential to find the most optimal practice in different regions. In this context the RIKS-HIA registry offers a unique possibility to follow this interesting topic.

In the present study 20% had rescue angioplasty and nearly 50% were revascularised within 14 days of theprehospital treated patients and the rate of early invasive procedures increased during the study period. A strategy of early invasive procedures within 24 hours compared with conservative management following thrombolytic treatment has been shown to favor the former strategy. Thus, a liberal use of early (within 24 hours) invasive procedures or at least within 14 days in PHT patients, is likely to result in a decreased rate of re-infarctions and improved long-term outcome. To implement such a strategy, all PHT treated patients should preferably be transported directly to interventional hospitals as in the CAPTIM study. Although recently tested routine PCI very early after fibrinolytic treatment failed to improve outcome (ASSENT-4 data presented at the ESC-meeting in Stockholm, September -05), a beneficial value of rescue angioplasty has been proposed in modest- to high-risk patients with an occluded IRA following thrombolysis. The most common method used to identify these patients is to evaluate ST-resolution. However, <50% ST-resolution within 60 minutes predicts IRA occlusion in only 50-60% of the cases and constitute a marker of failed tissue level reperfusion despite a patent IRA in the rest of the cases. An interesting option might be to add information on admission NT-proBNP and concentrate the effort on the high risk group with NT-proBNP elevation and no ST-resolution (about 25% of the patients without ST-resolution in our study) since the majority of the patients without ST-resolution (75% in our study) could be stratified to a lower risk group as indicated by no BNP elevation. Such a risk stratification and treatment strategy needs of course to be tested in a prospective trial.

Trial and non-trial patients

Our study could demonstrate a selection of less critically ill patients to a clinical trial of fibrinolytics, which point out the need for a more representative enrollment in clinical trials of acute MI consistent with previous studies. Interestingly, compared with men there was a higher mortality difference among women not enrolled versus enrolled in the trial after controlling for other risk factors including age. These relations have previously not been described and indicate that the selection of lower risk patients to the trial seemed to be more pronounced among women. To some extent, this might explain why women have been shown to have a worse outcome after AMI in many registry studies with unselected patients in contrast to some clinical trials. Moreover, this might further explain the lack of benefit for certain
treatments such as early revascularisation in UAP among women in randomised trials. Indeed, women compared with men included in the FRISC-2 trial had a lower prevalence of previous cardiac disease and elevated tnt. Thus, our finding implies that not only more women need to be included in clinical trials, but also that it is important to include a more representative population of women.

Information on the natural course, risk stratification scores and effects of new treatment strategies in STEMI also need to be accumulated from a broader perspective than what is reported from randomised clinical trials. For example, the risk index by Morrow and colleges for patients with STEMI treated with fibrinolytics was derived from a randomised trial and applied on an unselected registry population with the same treatment and STEMI aged over 65 years and found to be of limited value. In contrast, this index provided good quality risk stratification when applied on our randomised trial population. Thus, the prognostic value of admission NT-proBNP, tnt and early ST-resolution must also be validated in community based cohorts.

Patients with the strongest risk factors for mortality were the least likely to receive the favorable treatment with PHT in our study. A similar finding was reported from a large US-registry regarding variables at baseline influencing the use of reperfusion treatment or not. Hence, by providing PHT to more high risk patients, a larger benefit of the treatment could probably be achieved. This is a good example of that registries provide incremental information on the implementation of treatments.

Finally, another example of the need for studies in consecutive real life patients with STEMI was the finding that the in-hospital treatment delay in some randomised studies evaluating prehospital thrombolysis was unexpectedly short in contrast to our study. This finding could be explained by the fact that the conduct of these studies led to a marked shortening of time to thrombolysis once in hospital. As a consequence, the time saved by prehospital treatment was probably underestimated.
SUMMARY AND CONCLUSIONS

In patients with ST-elevation myocardial infarction treated with thrombolysis:

- Troponin T on admission and ST-resolution at 60 minutes are strong predictors of mortality and the combination of them gives additive early information on prognosis and further improves risk stratification.

- Admission NT-proBNP and troponin T seem to reflect in part similar mechanisms in relation to mortality as indicated by a moderate correlation in contrast to the weak correlations between ST-resolution at 60 minutes and both NT-proBNP and troponin T.

- NT-proBNP on admission is a strong independent predictor of long-term mortality and when evaluated together with admission troponin T and ST-resolution at 60 minutes, both NT-proBNP and early ST-resolution remains independently associated with mortality in contrast to troponin T. The combination of NT-proBNP and ST-resolution at 60 minutes gives complementary early information on prognosis and provides the best prediction of one-year mortality.

- Prehospital diagnosis and treatment reduce the time to thrombolysis by almost one hour, are associated with better left ventricular function and fewer complications and reduce the adjusted one-year mortality with 30% among real life patients. Compared to regular in-hospital thrombolysis, prehospital management with trained paramedics in the ambulances can substantially reduce mortality and morbidity.

- Patients treated with fibrinolytics and not enrolled in a clinical trial have higher risk characteristics and more early complications although the treatments provided are similar compared to those enrolled. The short- and long-term mortalities are almost twice as high in patients not enrolled in the trial even after adjustment for a number of risk factors. The major reason for the difference in adjusted outcome seems to be a selection of less critically ill patients to the trial.
Hjärt-kärl sjukdom är den vanligaste orsaken till död i den industrialiserade världen. En av dess mest dramatiska manifestation är akut hjärtinfarkt som beror på ett plötsligt stopp av blodflödet i ett av hjärtats kranskärl orsakat av en blod propp. I detta läge gäller det att så fort som möjligt återställa blod flödet för att minska skadan på hjärtmuskeln. Den vanligaste, enklaste och mest spridda metoden att göra detta är med proplösande läkemedel, så kallade trombolytika. Trots framgången med införandet av trombolysbehandling och annan modern hjärtinfarktsbehandling, varierar risken att dö till följd av en akut hjärtinfarkt högst påtagligt. En tidig risk bedömning av varje patient är därför viktig för att identifiera högrisk patienter och tidigt erbjuda dessa den bästa möjliga behandling samt att undvika onödiga och potentiellt riskfyllda behandlingar av lägrisk patienter. Tiden från symtomdebut till trombolysbehandling har stor betydelse för prognos vid hjärtinfarkt och i randomiserade studier har trombolysbehandling redan i ambulansen (prehospital) jämfört med på sjukhuset visat sig minska tiden till behandling och minska dödligheten. Värden av prehospital trombolys i den kliniska verkligheten bland oselekterade patienter är dock bristfälligt undersökta.

Implementationen av ny behandling, baserade på resultaten av stora kliniska studier, har minskat dödligheten efter akut hjärtinfarkt under de senaste decennierna. Det har emellertid ifrågasatts hur pass representativa dessa studier är. Exempelvis har flera stora kliniska studier gällande trombolytiska medel vid akut hjärtinfarkt uppsatt en imponerande låg dödlighet medan dödligheten varit betydligt högre i olika register studier av oselekterade patienter med samma behandling och diagnos.

Syftet med avhandlingen var att i en grupp patienter med akut hjärtinfarkt undersöka hur blodnivåerna av markörer för hjärtmuskelskada (troponin T) och nedsatt hjärtfunktion (proBNP) vid ankomst och graden av snabb återgång av ST-höjningen på EKG (ST-resolution) 60 minuter efter insatt trombolys behandling kan förutsäga risken att avlida (ca. 800 patienter). Vi ville också undersöka tid till behandling och dödlighet i relation till prehospital trombolys eller trombolys givet på sjukhus i en grupp oselekterade ambulanstransporterade hjärtinfarkts patienter (ca. 5400 patienter). Slutligen ville vi utvärdera riskfaktorer, behandlingar, komplikationer och dödlighet hos patienter som inkluderades i en trombolysstudie och hos patienter som
också behandlades med trombolys på samma sjukhus men inte togs med i studien (ca. 3700 patienter).

Förhöjda nivåer av troponin T och proBNP vid ankomst samt utebliven ST-resolution 60 minuter efter ankomst ökade påtagligt risken för död på kort och lång sikt. Kombinationen av förhöjt proBNP och utebliven ST-resolution gav den högsta risken för död, 26.2%, medan patienter med normalt proBNP och ST-resolution endast hade en dödlighet på 1.7% inom ett år.

Att ställa diagnosen akut hjärtinfarkt redan i ambulansen och påbörja trombolysbehandlingen där, istället för att diagnostisera och behandla på sjukhuset, minskade tiden från symtom debut till trombolysbehandling med nästan en timme hos en stor grupp oselektade patienter. Dessutom minskade andelen patienter med tidiga symtom på hjärtsvikt och hjärtats pumpförmåga var generellt bättre hos de som fått tidigare behandling i ambulansen. En trolig förklaring till detta är att den tidigare givna propplösande behandlingen redan i ambulansen kunnat rädda delar av hjärtmuskeln som annars hade skadats för alltid. Slutligen visade vår studie att de som trombolysbehandlats i ambulansen hade en 30% lägre dödlighet ett år efter hjärtinfarkten jämfört med de sjukhusbehandlade, efter justering för olikheter i riskfaktorer, ålder och kön.

Vid jämförelsen av patienter som fick trombolysbehandling och togs med i en klinisk trombolysstudie med de som inte togs med i studien på samma sjukhus, framkom att studiepatienterna var yngre, hade färre kvinnor, färre riskfaktorer och färre tidiga komplikationer jämfört icke-studiepatienterna. Efter justeringar för olikheter i riskfaktorer, ålder, kön och tidiga tecken till hjärtsvikt var ändå dödligheten nästan dubbelt så stor hos de patienter som inte togs med i studien jämfört med de som togs med. En avgörande orsak till den stora skillnaden i dödlighet verkade vara en selektion av mindre svårt sjuka patienter till studien.
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