The ECG as Decision Support in STEMI

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The present thesis is based on the following original peer reviewed publications. The publications are referred to by their roman numerals.

Study I. Maria Sejersten, Olle Pahlm, Jonas Pettersson, Peter Clemmensen, Farida Rautaharju, Sophia Zhou, Charles Maynard, Charles L. Feldman, and Galen S. Wagner. The relative accuracies of ECG precordial lead waveforms derived from EASI leads and those acquired from paramedic applied standard leads. J Electrocardiol 2003,36:179-185.

Study II. Maria Sejersten, Dwayne Young, Peter Clemmensen, Jonathan Lipton, Debra VerSteeg, Thomas Wall, Charles Maynard, and Galen S. Wagner. Comparison of the ability of paramedics with that of cardiologists in diagnosing ST-segment elevation acute myocardial infarction in patients with acute chest pain. Am J Cardiol 2002;90:995-998.

Study III. Maria Sejersten, Martin Sillesen, Peter Riis Hansen, Søren Loumann Nielsen, Henrik Nielsen, Sven Trautner, David Hampton, Galen S. Wagner, and Peter Clemmensen. Effect on treatment delay of prehospital teletransmission of 12-lead electrocardiogram to a cardiologist for immediate triage and direct referral of patients with ST-segment elevation acute myocardial infarction to primary percutaneous coronary intervention. Am J Cardiol 2008;101:941-946.

Study IV. Maria Sejersten, Rasmus S. Ripa, Charles Maynard, Peer Grande, Henning Rud Andersen, Galen S. Wagner, and Peter Clemmensen, for the DANAMI-2 investigators. Timing of ischemic onset estimated from the electrocardiogram is better than historical timing for predicting outcome after reperfusion therapy for acute anterior myocardial infarction: A DANish trial in Acute Myocardial Infarction 2 (DANAMI-2) substudy. Am Heart J 2007 Jul;154:61.e1-61.e8.

Study V. Maria Sejersten, Rasmus S. Ripa, Charles Maynard, Galen S. Wagner, Henning Rud Andersen, Peer Grande, Leif Spange Mortensen, and Peter Clemmensen, for the DANAMI-2 investigators. Usefulness of quantitative baseline ST-segment elevation for predicting of outcomes after primary coronary angioplasty or fibrinolysis (Results from the DANAMI-2 trial). Am J Cardiol 2006,97:611-616.

Study VI. Maria Sejersten, Søren Loumann Nielsen, Thomas Engstrøm, Erik Jørgensen and Peter Clemmensen. Feasibility and safety of prehospital administration of bivalirudin in patients with ST-elevation myocardial infarction. Am J Cardiol 2009,103:1635-1640.

Study VII. Maria Sejersten, Nana Valeur, Peer Grande, Torsten Toftegaard Nielsen, and Peter Clemmensen for the DANAMI-2 Investigators. Long-term prognostic value of ST-segment resolution in patients treated with fibrinolysis or primary percutaneous coronary intervention: Result from the DANAMI-2 (DANish trial in Acute Myocardial Infarction-2). J Am Coll Cardiol 2009;54:1763-1769.

ABBREVIATIONS AND ACRONYMS

ACE: Angiotensin converting enzyme
ACS: Acute coronary syndrome
ACUITY: Acute catherterization and urgent intervention triage strategy
AF: Atrial fibrillation
AMI: Acute myocardial infarction
AW: Anderson Wilkins
BMI: Body mass index
CABG: Coronary artery bypass grafting
CARESS-in-AMI: Combined abciximab reteplase stent study in acute myocardial infarction
CCU: Cardiac care unit
CKMB: Creatinin kinase myocardial band
DANAMI-2: Danish trial in acute myocardial infarction 2
ECG: Electrocardiogram
ED: Emergency department
EF: Ejection fraction
EMS: Emergency medical system
EMT: Emergency medical technician
EUROMAX: European ambulance acute coronary syndrome angiox
FINESSE: Facilitated intervention with enhanced reperfusion speed to stop events
GI: Grades of ischemia
GISSI: Gruppo italiano per la sperimentazione della streptochinasi nell'Infarto miocardico
GPI: Glycoprotein IIb/IIIa inhibitor

GUSTO: Global utilization of strategies of open occluded coronary arteries
HORIZONS-AMI: Harmonizing outcomes with revascularization and stents – acute myocardial infarction
IQR: Inter-quartile range
IRA: Infarct related artery
ISIS-2: Second international study of infarct survival
LBBB: Left bundle branch block
LCD: Liquid crystal display
LVH: Left ventricular hypertrophy
MACE: Major adverse cardiac events
MI: Myocardial infarction
ML: Mason-Likar
MRI: Cardiac magnetic resonance imaging
NRMI: National registry of myocardial infarction
On-TIME: Ongoing tirofiban in myocardial infarction evaluation
PATS: Patient analysis and tracking system, Dendrite Systems
PCI: Percutaneous coronary intervention
PET: Position emission tomography
PEA: Pulseless electrical activation
PRAGUE-2: Primary angioplasty in patients transferred from general community hospitals to specialized PTCA units with or without emergency thrombolysis 2
pPCI: Primary percutaneous coronary intervention
PPV: Positive predictive value
RBBB: Right bundle branch block
RVH: Right ventricular hypertrophy
SPECT: Single photon emission computed tomography
STEMI: ST-segment elevation myocardial infarction
STREAM: Strategic reperfusion early after myocardial infarction
TAPAS: Thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction study
TIMI: Thrombolysis in myocardial infarction
TRANSFER-AMI: Trial of routine angioplasty and stenting after fibrinolysis to enhance reperfusion in acute myocardial infarction
VF: Ventricular fibrillation
VT: Ventricular tachycardia

CHAPTER 1

INTRODUCTION AND AIMS

Ischemic heart disease is a leading cause of death and disability. Every year ischemic heart disease causes more than 46.000 admissions to hospitals in Denmark, and nearly 16.000 are diagnosed with acute myocardial infarction (AMI). (1) Among patients diagnosed with AMI, some have electrocardiographic (ECG) changes meeting the criteria for ST-segment elevation myocardial infarction (STEMI). Guidelines have been developed to classify patients with STEMI, but the criteria are continuously changing as the diagnostic abilities are enhanced. (2-4) Likewise, advantages in the treatment of STEMI patients including new medications and invasive procedures have evolved. Remaining challenges include optimizing these therapies in the individual patient presenting with symptoms and ECG changes suggesting STEMI.

The ECG is pivotal in providing diagnostic decision support for this large group of patients, because the clinical symptoms are non-specific and biochemical markers are often not yet elevated at the time of patient presentation. The standard 12-lead ECG is valuable for determining presence, location, and extent of jeopardized myocardium during acute coronary occlusion.(3;4) However, more specific ECG methods could potentially lead to therapeutic decisions that would provide the optimal prognosis for each individual with STEMI.

The recording of an accurate standard 12-lead ECG in the ambulance is the first step in optimizing treatment in patients with chest pain, since the ECG is the foundation for an immediate diagnosis and subsequent therapeutic interventions and/or further diagnostic tests. As soon as patients' presenting 12-lead ECG indicates STEMI, the key therapeutic decision is to initiate intravenous thrombolytic therapy, or rapid transportation to a catheterization laboratory for primary percutaneous coronary intervention (pPCI). If this latter method is selected, the delay until it can be performed requires ECG monitoring to provide decision support for managing clinical complications, and for providing interim antithrombotic therapy. Regardless of reperfusion strategy, serial ECG changes can be used to determine the completeness of the patient's response to therapy and thereby be used as the basis for decisions regarding further interventions such as percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). In conclusion, a number of decisions must be made in the process of treating STEMI patients.

This thesis aims at optimizing the decision support, provided by the ECG, for choosing the best treatment strategy in the individual STEMI patient:

Accurate prehospital ECG recording

Acquiring an early accurate prehospital 12-lead ECG – by evaluating an alternative and simple ECG lead system (Study I).

Correct prehospital ECG diagnosis for early triage and reperfusion therapy

Ensuring an early correct prehospital ECG diagnosis – by comparing the ability of paramedics to that of a cardiologist in diagnosing STEMI (Study II).

Assuring early triage and minimal treatment delay – by transmission of prehospital ECG directly to the attending cardiologist's mobile phone (Study III).

The ECG as decision support for choice of reperfusion therapy

Determining whether the initial ECG can identify patients who will benefit greatly from acute reperfusion therapy versus patients with modest effect – by focusing on ECG timing of coronary artery occlusion (Study IV).

Determining whether initial ST-segment elevation can assist in choosing type of treatment strategy – by predicting outcome in patients treated with pPCI versus fibrinolysis (Study V).

The ECG for monitoring and initiating antithrombotic therapy for optimal prehospital care

Evaluating safety during ambulance transport – by assessing the complication rate in patients transferred directly to a tertiary hospital for pPCI (Study III).

Ensuring most favorable prehospital therapy – by determining the efficacy and safety when substituting prehospital heparin with bivalirudin (Study VI).

The ECG as decision support for further therapy after initial reperfusion

Evaluating whether post-procedure ECG can be used as decision support for further treatment – by determining the prognostic value of ST-segment resolution in patients treated with pPCI versus fibrinolysis (Study VII).

CHAPTER 2

THE STANDARD ELECTROCARDIOGRAM

Since the first recording of electrical activity in the human heart by the English physiologist Augustus Désiré Waller in 1887 (5), and the Dutch physiologist Willem Einthoven's development of the sensitive string galvanometer for more than 100 years ago (6), the ECG has become a valuable, inexpensive, non-invasive tool assisting the clinician in diagnosis, decision support of treatment strategy, monitoring treatment efficacy, and risk stratification in patients with myocardial ischemia or infarction.

ECG waveforms

The constantly changing electrical currents in the heart are the foundation for the recording of an ECG. A total of 10 electrodes (3 limb electrodes, 6 precordial electrodes, and 1 ground electrode) are required for recording the standard 12 ECG leads. The six limb leads (I, II, III, aVR, aVL, and aVF) view the heart in the frontal plane, while the 6 precordial leads (V1-V6) view the heart in the transverse horizontal plane (Figure 1a and 1b). All leads are bipolar, but only lead I, II and III use 2 independent electrodes - a positive and a negative limb electrode. The 3 aV (argumented) limb leads are recorded from a positive limb electrode and a negative electrode provided by the average inputs from the remaining 2 limb electrodes. The 6 precordial leads are recorded from one independent positive precordial electrode and a negative electrode provided by Wilson's central terminal -averaged inputs from the 3 limb electrodes. (4) Each ECG lead reflects both positive and negative views of the summation of all electrical impulses spreading through the heart for every cardiac cycle. The resultant electrocardiographic recording consists of the: P-wave, P-Q segment, Q-, R-, and S-wave (QRS complex), ST-segment, T-wave, and T-P segment. These waveforms represent first the activation of the atria (P-wave), secondly the activation of the ventricles (QRS complex), and finally ventricular recovery (T-wave). As a consequence of the conventional placement of the electrodes over a normal leftward situated heart the recording will mainly produce a positive reflection. The exceptions are leads aVR and V1 with the poles oriented rightward.

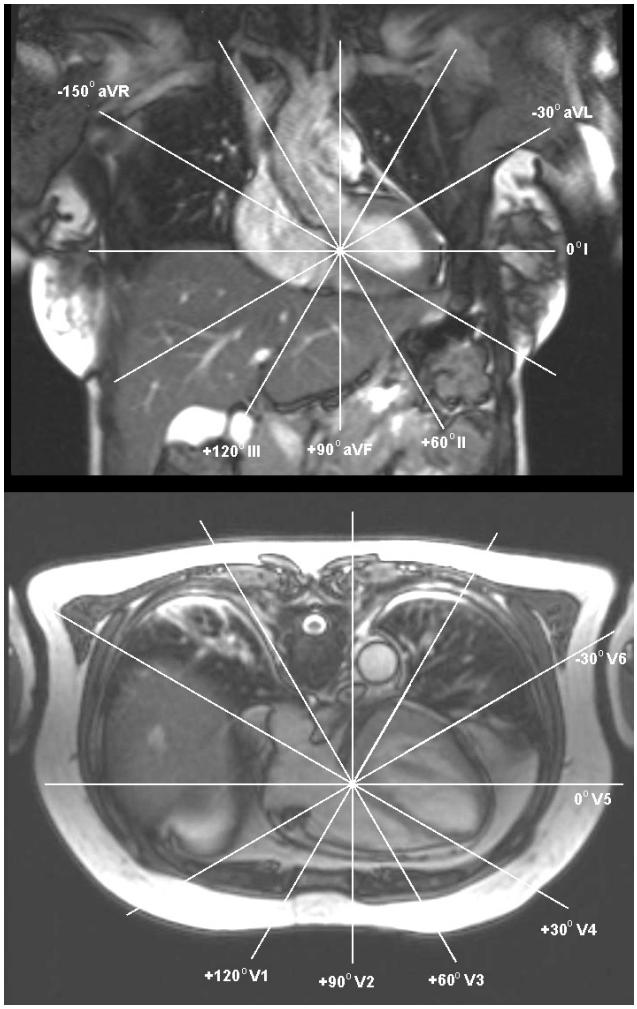

Figure 1

(A) The locations of the positive and negative poles of each limb lead in the frontal plane around the 360 degrees of the "clock face". The names of the leads appear at their positive poles.
(B) The locations of the positive and negative poles of each precordial lead in the horizontal plane around the 360 degrees of the "clock face". The names of the leads appear at their positive poles.

Waveform changes caused with ischemia reflect its presence, location, extent, severity and timing. Presence, location, and extent of ischemia are indicated by changes in the ST-segment, while severity is indicated by distortion of the QRS complex, and timing by the occurrence of tall T-waves versus abnormal Q-waves in leads with ST-segment changes. (3;4)

In a normal ECG the ST-segment is isoelectric or nearly isoelectric, but in the presence of an injury current generated by the difference in gradients across the boundary between normal and transmurally ischemic myocardium, the ST-segment will move towards the involved myocardial region. Consequently, the direction of the ST-segment changes will depend on the orientation of the affected myocardial region in relation to each individual lead. In the conventional ECG, involvement of anterior or inferior regions of the myocardium will then be recognized as ST-segment elevation. In contrast, posterior-lateral involvement (caused by occlusion of the left circumflex artery) will produce ST-segment depression and thereby never meet STEMI criteria, which suggests that a diagnosis of ischemia/infarction is indicated when the ST-segment reaches a predetermined threshold value in 2 or more anatomically contiguous ECG leads. (3;4)

Not only the extent of the ischemia, but also other variables such as the distance between the heart and chest wall and the width of the chest wall may influence the magnitude of ST-segment elevation. Additionally, ST-segment elevation may also be caused by other abnormalities e.g.: acute pericarditis, elevated potassium levels, left ventricular hypertrophy, right or left bundle branch block (RBBB, LBBB), Brugada syndrome, acute myocarditis, cardiac tumors, and the normal variant "benign early repolarization". (3)

ST-segment elevation is associated with reciprocal ST-segment depression in leads in which the positive electrode is directed in the opposite direction (≈180° away from). For example, ST-segment elevation in lead III (positive electrode is pointed rightward and inferiorly) is associated with ST-segment depression in lead aVL (the positive electrode is pointed leftward and superiorly) and vice versa. (4) This ST-segment depression should be considered a STEMI equivalent.

Changes in the QRS complex are seen with severe ischemia and infarction. (7;8) When the ischemia is severe because of poorly protected myocardium, the QRS complex is directed towards the

ischemic region, but then shifts away from the region revealing abnormal Q-waves as infarction develops. The presence of abnormal Q-waves is usually pathognomonic of a prior myocardial infarction (MI). (9) They represent loss of electrical activity from necrotic cells and are therefore a sign of cell death.
Tall T-waves, directed toward the epicardial surface in the center of the ischemic area, are seen in the early stages of ischemia. The mechanism behind tall T-waves is not fully clarified but may be associated with an increase in intercellular potassium, which then shorten the action potential duration in the ischemic zone and causes early repolarization. (10;11) In contrast, late repolarization causes negative T-waves seen later in the ischemic process as an indication of successfully reperfusion of the myocardium. (11)
Based on the mentioned changes in ECG waveforms, 4 phases of serial ECG changes during acute coronary occlusion have been described: Hyperacute, Acute, Sub-acute, and Chronic (Figure 2). (12) The time courses of the phases differ in each individual, and will be delayed during gradual coronary occlusion, but accelerated with prompt occlusion. In general the ischemic process is potentially reversible in the hyperacute phase, while progressive infarction occurs throughout the acute phase. Consequently, jeopardized myocardium can potentially be salvaged from undergoing infarction in the earliest phases of coronary occlusion, while no significant salvage will occur during the subsequent phases. The benefit of initiating reperfusion therapy during the later phases is thus prevention of infarct extension, and enhancement of the healing process.

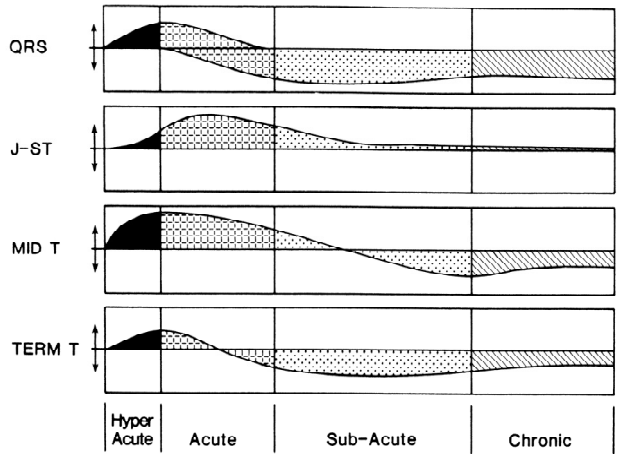

Figure 2
The diagram shows the 4 ECG phases of acute coronary occlusion. At the bottom the evolution of the acute infarct to its chronic phase is indicated. Each panel illustrates the typical change in direction and amplitude of the QRS complex, ST-segment at the J-point, and mid and terminal T-waves. A shift toward the ischemic/infracted area is indicated by an upward-pointing arrow, while a shift away from this area is indicated by a down-ward-pointing arrow.
Reprinted from Acute coronary care in the thrombolytic era.12 With permission from G. S. Wagner.

Myocardial salvage
Myocardial salvage is a term used for the amount of myocardium at risk that does not undergo infarction due to e.g. spontaneous reperfusion or initiation of reperfusion therapy. The amount of myocardium salvaged by initiation of reperfusion therapy may then be a measure for reperfusion success. A salvage index was first proposed by Clemmensen et al. (13) by subtraction the final estimated infarct size from the initially predicted area at risk for infarction. Myocardium at risk can be predicted by the Aldrich score, which is based on ST-segment elevation on the initial ECG. (14) The score is a measure of the initially predicted myocardial infarct size as a percentage of the left ventricle if no reperfusion treatment is initiated. The original formula has been validated for anterior AMI but changed for inferior AMI. (15)
The final infarct size can be estimated on the predischarge ECG by use of the Selvester QRS score. (16) This score contains 50 criteria considering Q- and R-wave durations, and relative Q-, R- and S-wave amplitudes. It awards a maximum of 31 points, each representing approximately 3% infarction of the left ventricle. A high QRS score implies more extensive transmural myocardial damage. This scoring system was originally developed from anatomic studies of anterior and inferior infarcts, and has since been validated using single photon emission computed tomography (SPECT) (17), and delayed enhancement cardiac magnetic resonance imaging (MRI). (18)
In conclusion, the acute changes in the ECG waveforms can provide clinicians with essential information when evaluating patients presenting with chest pain. The 12-lead ECG may therefore be very useful as decision support and help optimize treatment in this large group of patients.

ACUTE MYOCARDIAL INFARCTION
Myocardial infarction develops as myocardial cells die due to prolonged myocardial ischemia. The most common mechanism behind AMI is disruption of an atherosclerotic plaque causing activation, adhesion, and aggregation of platelets, and release of vessel contractive substances, and formation of a thrombotic occlusion. Less often forms the occluding thrombus from a superficial erosion of the endothelial surface. (19) The sudden complete coronary occlusion causes immediate ischemia in the myocardium due to inadequate flow of oxygenated and nutrient-enriched blood compared to the myocardial oxygen demands. Several factors can alter the time available before irreversible damage to the myocardium occurs including: collaterals to the ischemic area, metabolic ischemic preconditioning, and persistent versus intermittent coronary artery occlusion.
Both collaterals interconnecting epicardial arteries and preconditioning may develop in various degrees depending on prior ischemic episodes in the individual. (20;21) Accordingly, the degree of ST-segment elevation has been shown to be markedly reduced in hearts preconditioned with ischemia and/or in hearts with rich collateral arterial flow. (8) In addition marked prolongation of the QRS complex seen with severe ischemia are decreased in preconditioned hearts. (8) The mechanisms of metabolic preconditioning are not fully clarified, but may be a humoral and/or neural response to the ischemic state which then increases the myocardium's tolerance to ischemia at later episodes. Interestingly, preconditioning has been shown to produce pronounced action potential duration shortening (22), and thereby tall T-waves may be a result of preconditioning, especially when present after a prolonged period of ischemia. Even in the presence of the mentioned cardiac protective factors jeopardized myocardial tissue will undergo infarction if adequate reperfusion treatment is not established in a timely manner.

TREATMENT IN STEMI

The goal in treating STEMI patients is to reduce morbidity and mortality by ensuring an early and correct diagnosis, and appropriate triage with early initiation of treatment of the acute event, but also by improving both management of complications, and availability of pharmacologic and mechanical reperfusion therapies.

Continuous advancements within medicine have enhanced the chances of survival after STEMI. In the 1960s patients surviving the acute event were hospitalized for several weeks as bed-rest was thought to reduce myocardial demand and thereby better prognosis. With the establishment of coronary care units (CCU) in the 1960s, and the use of advanced equipment for monitoring and defibrillation, mortality slowly decreased. (23) Aspirin was introduced in the 1980s as the first pharmacological treatment targeting the acute event and reduced cardiac mortality by 24%. (24) Mortality rates were further reduced by initiation of pharmacological reperfusion therapy in the mid 1980s (25), and mechanical catheter-based interventions in the 1990s. (26) Additionally, β blockers (27), angiotensin-converting enzyme (ACE) inhibitors (28), and statins (29) have contributed to improve long-term prognosis in STEMI patients. The present 30-day mortality rate in Denmark is historically low at 6.8% for STEMI patients undergoing pPCI (30), but the hope is to improve the prognosis further by using information technology, and the ECG to optimize treatment and decision support in the individual patient.

Importance of time

The benefit of reperfusion therapy is time dependent and decrease exponentially with the largest benefit seen within the first hours after symptom onset. This was first illustrated by Boersma et al. (31) in a meta-analysis of 22 randomized trials comparing thrombolytic therapy versus placebo. A reduction in mortality was highest in patients presenting within 1 hour after symptom onset, while the treatment benefit was reduced over time according to a non-linear model. The term *"Golden hour"* became widespread, and challenged clinicians to initiate fibrinolytic treatment shortly after symptom onset. Likewise, De Luca et al. (32) showed that mortality also increased with time delay in patients undergoing pPCI. A metaanalysis of randomized trials comparing fibrinolysis versus pPCI have confirmed that time delay is important in both treatment regimes. (33)

Pharmacological reperfusion

Pharmacological reperfusion is the most widely available reperfusion method. The Gruppo italiano per la sperimentazione della streptochinasi nell'Infarto miocardico (GISSI) (34), and the second international study of infarct survival (ISIS-2) (35) were the first to show that thrombolysis was superior to conservative treatment. This was supported by a meta-analysis including 9 randomized trials showing that morbidity and mortality in STEMI patients was substantially reduced with thrombolysis. (25) Depending on when the diagnosis is established and what is common practice in a particular area thrombolysis can be initiated either in the prehospital setting or at hospital arrival. Hospital thrombolysis can be initiated 40 minutes sooner if a prehospital diagnosis is established by ECG and used for early notice and triage directly to the CCU. (36) A meta-analysis showed that when thrombolysis is established in the prehospital setting time from symptom onset to initiation of treatment can be reduced with up to 58 minutes, and that this reduction translates into a reduction in 30-day mortality rate (10.2% to 8.6%;p=0.03). (37) However, not all patients are eligible for thrombolysis due to contraindications or long symptom duration beyond 12 hours. An alternative for such individuals is mechanical reperfusion.

Mechanical reperfusion

The technique of inserting a catheter though a systemic artery for balloon inflation and dilation of a stenotic artery was first introduced in man by Grüntzig in 1977. (38) Since then the technique and equipment have developed tremendously from an elective therapeutic alternative to CABG in patients with chronic coronary artery disease to an acute procedure in patients presenting with STEMI. (39) Mechanical reperfusion by pPCI is defined as angioplasty with or without stenting, but with no prior or concomitant fibrinolytic therapy. Primary PCI is effective in securing and maintaining coronary artery patency and avoids some of the bleeding risks seen with thrombolysis. However, worldwide it is not as generally available as thrombolysis, since it must be performed in hospitals with an experienced team of interventional cardiologists, and skilled supporting staff in order to diminish adverse outcomes. (40) With only highly specialized hospitals offering pPCI, the ambulance is the ideal place for early diagnosis and triage followed by direct transfer of STEMI patients to a catheterization laboratory bypassing local hospitals.

DANAMI-2

Controversies regarding the best method of reperfusion therapy lead to the Danish trial in acute myocardial infarction-2 (DANAMI-2). (41-43) This is the largest randomized trial comparing outcome in on-site fibrinolyzed patients versus patients either transported or admitted directly to a tertiary hospital for pPCI. Patients were included from December 1997 to October 2001. Twenty-four referral hospitals and 5 tertiary hospitals with 24-hour pPCI service participated in the study. These hospitals served 62% of the Danish population. All patients admitted to a hospital with symptoms suggestive of STEMI for more than 30 minutes but less than 12 hours, and cumulated ST-segment elevation of ≥4 mm were eligible for enrolment. Catheterization laboratory arrival was to be ≤3 hours in patients randomized at referral hospitals, and ≤2 hours in patients randomized at tertiary hospitals.

All patients received aspirin, β-blocker and an intravenous bolus of unfractionated heparin. Patients randomized to fibrinolytics received accelerated treatment with the tissue plasminogen activator alteplase. Patients randomized to pPCI received angiography followed by treatment of the infarct related artery (IRA) if it was totally occluded, if the culprit lesion had a stenosis >30% of the lumen, or if thrombolysis in myocardial infarction (TIMI) flow was <3. Stenting was applied in all vessels with a diameter >2.0 millimeters. Glycoprotein IIb/IIIa inhibitors (GPI) were administered at the PCI operators' discretion.

A total of 1572 patients were included in the study, with 1129 randomized at referral hospitals and 443 at tertiary hospitals. Four percent of patients screened at referral hospitals were excluded because they were considered unstable for transport. The assigned treatment was applied in 99% of cases in the fibrinolytic group, and in 98% of cases in the angioplasty group (87% had balloon inflation).

Median time from onset of symptoms to start of fibrinolysis was 169 minutes (inter-quartile range ([IQR] 110-270 minutes) compared to 224 minutes (IQR 171-317 minutes) for patients transferred to angioplasty. Consequently, angioplasty was related to a median treatment delay of 50 minutes (IQR 39-65 minutes). Transport distance from referral hospitals to tertiary hospitals

was median 50 kilometers (range 3-150 kilometers), and lasted median 32 minutes (IQR 20-45 minutes).
The trial showed a 40% (8.5% versus 14.2%; p=0.002) relative reduction in the composite endpoint at 30-days with pPCI in referred patients versus on-site fibrinolytics. The outcome was primarily driven by a significant reduction in reinfarction rate (1.6% versus 6.3%; p<0.001). Small reductions in death and stroke rates were seen in the pPCI group, but these were not statistically significant. Ninety-six percent of patients were transferred from a local hospital to a tertiary hospital for pPCI within 2 hours. The benefit of pPCI was the same in transferred patients and patients admitted directly to a tertiary hospital. The superiority of transfer for pPCI was sustained at 3 years (composite endpoint: 20.1% versus 26.7%; p=0.007). (44) Additionally, pPCI significantly reduced the rates of clinical reinfarction, coronary revascularization, and readmission for cardiac disease at 3 years. (44)
The higher reperfusion rates and better prognosis with pPCI seen in DANAMI-2 were confirmed by metaanalyses. (26;33) Apparently, the superiority of pPCI was independent of both the type of thrombolytic agent, and whether or not the patient was transferred acutely for pPCI. As a result of these findings the recommended reperfusion strategy for STEMI patients has shifted towards pPCI in many places, including Denmark where the DANAMI-2 trial has had special impact on the prehospital treatment strategy and triage of STEMI patients.

Reperfusion strategy in patients presenting early versus late
Several reports have suggested similar mortality rates in patients receiving thrombolytic therapy and pPCI within 2-3 hours of symptom onset, whereas pPCI is superior in patients presenting between 3-12 hours. (45-47) The on-going Strategic reperfusion early after myocardial infarction (STREAM) trial is intended to consolidate existing data showing that prehospital thrombolysis is not *second-best*, but rather can yield patient outcomes as good as, or even better than those obtained with pPCI. Patients with STEMI presenting within 3 hours after symptom onset, but unable to undergo pPCI within an hour will be randomized to prehospital fibrinolysis or pPCI. The results from this trial will be of great importance in the many places worldwide where early pPCI is not ready available, but ambulances can reach the patients early, initiate treatment, and transport the patients to a tertiary hospital for angioplasty and PCI if needed.
However, the pursuit to find the best reperfusion strategy for the individual patient should not end with population studies like DANAMI-2 or STREAM since results obtained from these large studies may not apply to all subsets of patients, and efforts should be put towards optimizing treatment in the individual patient.

STEMI guidelines
Based on the findings discussed above the European Society of Cardiology, the American Heart Association, and the American College of Cardiology have listed goals for transportation and initiating reperfusion treatment in STEMI patients. (48-50) Generally, thrombolysis should be started within 30 minutes and pPCI with 90 minutes from first medical contact. These goals should be considered the longest times acceptable and all efforts should be put toward keeping the total ischemic time less than 120 minutes, ideally 60 minutes, from symptom onset to initiation of reperfusion therapy. It is a great challenge to reach these goals since delays can arise in every step from symptom onset to initiation of reperfusion therapy. However, the key may be to establish an early diagnosis by ECG, preferable a prehospital ECG, as the basis for an early triage decision, and further treatment.
The recent Combined abciximab reteplase stent study in acute myocardial infarction (CARESS-in-AMI) (51), and the Trial of routine angioplasty and stenting after fibrinolysis to enhance reperfusion in acute myocardial infarction (TRANSFER-AMI) (52) showed that outcome in high risk patients initially treated by fibrinolysis was improved with a strategy of transfer to a tertiary hospital for coronary angiography and PCI a few hours after fibrinolysis. Based on these results the most recent international guidelines recommend that all high-risk patients treated with fibrinolysis as the primary reperfusion therapy at a non-PCI-capable facility receive appropriate antithrombotic therapy and transfer to a tertiary hospital where PCI can be performed either when needed, or as a pharmacoinvasive strategy. Guidelines also recom-mend that transfer is considered in low risk patients, especially if symptoms persist and failure to reperfusion is suspected. (50)

CHAPTER 3
ACCURATE PREHOSPITAL ECG RECORDING
With the goal of establishing an early diagnosis in STEMI, current guidelines recommend the recording of a 12-lead ECG by the emergency medical service (EMS) in all patients with chest pain, dyspnoea of unknown cause, and resuscitation after cardiac arrest. (48;49) However, this goal entails several challenges. First of all, only 50% of patients suspected of having AMI is brought in by ambulance. (53) Secondly, ambulances must be adequately equipped and manned with trained personnel to acquire high quality ECG with a minimum of prehospital time delay.
Correct prehospital diagnosis and triage relies on the quality of the 12-lead ECG recorded in the ambulance. However, the standard 10 electrode, 12-lead ECG may not be suitable for the prehospital setting, because it is time consuming, and a challenge for even skilled personnel to place the precordial electrodes at their correct positions based on skeletal landmarks identified by palpation. (54) In addition, the precordial electrodes may interfere with clinical procedures, while electrodes placed on the limbs produce disturbance of the baseline during patient movements. Consequently, recording of a standard 12-lead ECG with sufficient quality for reliable diagnostic purposes in the prehospital setting is virtually impossible with patients lying on a stretcher in a moving ambulance. With this in mind it must be decided, how accurate electrode placement can be secured, and whether the standard or an alternative ECG lead system should be used, so everyone involved in the care of a patient can rely on the recorded ECG for diagnostic purposes.

Precordial electrode placement
Accurate placement of the precordial electrodes is necessary in order to interpret the ECG correctly since even minor precordial electrode misplacements of 20-25 mm cause changes in QRS waveform morphology. (55;56) Herman et al. (56) showed that 2 cm deliberate misplacement of precordial electrodes in cranial or caudal direction produced significant Q-wave appearance/disappearance and/or significant ST-segment elevation/depression in 19% of patient. Such changes can impact patient care with large consequences for the individual patient.
Study I showed that a group of paramedics trained in ECG recording misplaced the precordial electrodes with a mean of 30 mm (range 18-39 mm) in a non-acute controlled setting. Lead V1

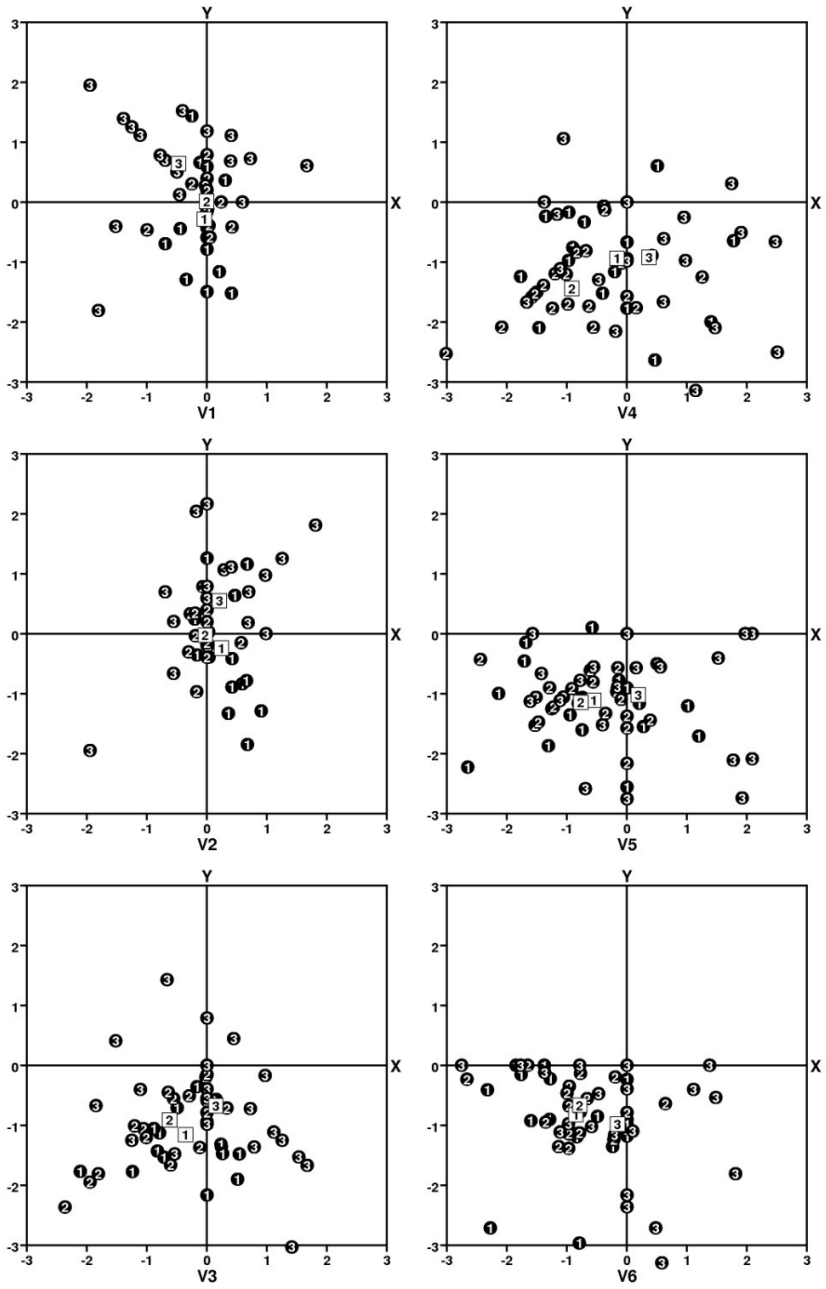

Figure 3
Precordial electrode placement in 60 cases. The plot shows displacements on a 1 inch grid. The numbers 1, 2 and 3 refer to by whom and in which setting the precordial electrodes were placed: 1) Paramedics in a non-acute experimental setting; 2) Electrocardiograph technician in the emergency department; 3) Paramedics in the field. Squared numbers indicate the mean misplacement in a given lead in the 3 different settings.
Reprinted from Sejersten et al. J Electrocardiol 2007;40:120-126.With permission from Elsevier.

and V2 were misplaced the least, while V5 were misplaced the most.

Typically, were the electrodes placed below and to the patient's right compared to the correct lead placement. The misplacement was also mean 30 mm when electrodes were placed by an emergency department (ED) technician (57), but increased to mean 37 mm when placed by paramedics in the prehospital setting (Figure 3). (58)

Rajaganeshan et al. (59) showed that cardiac technicians were by far the best to place the precordial electrodes correctly compared to nurses, non-cardiologist physicians, and cardiologists. Cardiologists performed the worst by placing the V1 and V2 electrodes

to high, often in 2nd intercostal space, and V5 and V6 in a line parallel to the ribs instead of in the horizontal plane as V4.

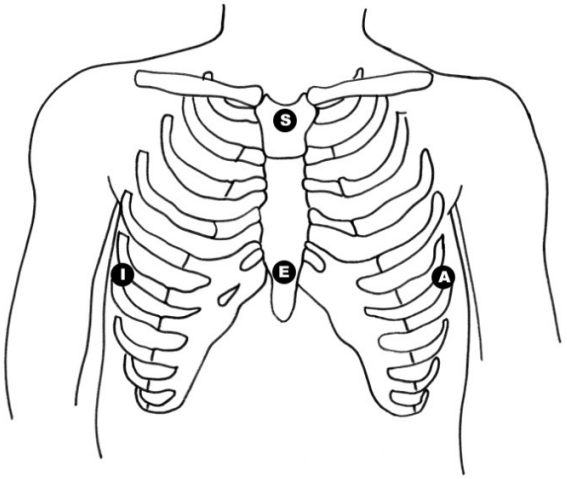

Figure 4
Location of the 4 EASI electrodes. A ground electrode can be placed anywhere on the body.
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As seen in a prior study (54), placement of lead V3-V5 in women was a particular problem in Study I. On the female chest, paramedics placed the electrodes on the chest wall immediately inferior to the left breast, instead of on the breast corresponding to the 5th intercostal space. The reason may be a general assumption that the breast tissue attenuates QRS waveform amplitudes. However, Rautaharju et al. (60) found that breasts only accounted for <1% of the variation in waveform amplitudes and recommended correct electrode placement corresponding to the 5th intercostal space. Besides misplacement of precordial electrodes, reversal of 2 electrodes can cause diagnostic difficulties. Lead reversal was identified in 4% of recorded ECG in a CCU. (61)

Limb electrode placement
For the recording of a standard 12-lead ECG the 3 limb electrodes must be placed on the limbs. Study I did not evaluate resultant waveform morphology after limb electrode placement by paramedics since precision is not required as long as the electrodes are placed on the distal part of each limb, and below the mid part of the upper arm and thigh. (62;63) However, with this standard placement, artifacts will appear in case of movements of the limbs. Consequently, in a moving ambulance, limb electrodes placed on the limbs are prone to result in a noisy signal.
There is a tendency of both paramedics and hospital staff to move the limb electrodes to torso positions, which is also the standard in monitoring. (64) The positions on the torso may vary in practice from the original Mason-Likar (ML) designations: arm electrodes in the infraclavicular fossa medial to the border of the deltoid muscle and 2 cm below the border of the clavicle; leg electrodes in the anterior axillary line, halfway between the costal margin and the crest of the ilium (65), because of the intention to produce more "extremity-like" waveforms. The move of the limb electrodes to the torso positions causes a rightward frontal plane axis shift accompanied by diminished Q-waves and thereby loss of evidence of prior inferior or posterior MI. (62;63) This change may be clinically relevant since it can lead to misdiagnosis. It is important to keep in mind that every time the limb electrodes are moved away from the distal extremities and placed on the torso the resultant ECG is no longer a standard 12-lead ECG.

The "EASI" lead system
To simplify electrode placement and save valuable time in the prehospital setting the EASI lead system (Phillips Medical System, Andover, Mass) may be an alternative to the standard 12-lead ECG. This alternative lead system was developed by Dower66 based on the vector ECG principles described by Frank. (67) The lead system consists of 4 chest electrodes (labeled E;A;S;I), and one reference electrode placed anywhere on the torso (Figure 4). The E electrode is placed on the lower extreme of the sternum, the S electrode on the manubrium sternum, and the A and I electrodes in the midaxillary line at the same horizontal line as the E electrode. A 12-lead ECG can be derived as the linear combination of the three EASI lead vectors: 1) Lead ES: S(-) to E(+), 2) Lead AS: S(-) to A(+), and 3) Lead AI: I(-) to A(+) using optimized fixed coefficients. (66;68) For example, at any instant the potential in lead I can be determined from the equation I =aES + bAS + cAI, where a, b, c are fixed coefficients and ES, AS, AI represents the potentials recorded in leads ES, AS, AI. Similar equations apply to all 12 leads but with different values of a, b, c. Lead ES views the heart's electrical activity from a caudal-cranial direction, but with a considerable anterior-posterior component. Lead AS views the heart's electrical activity both in the left-to-right, and caudal-cranial directions besides having a small anterior-posterior component. Finally, lead AI views the heart's electrical activity in a left-to-right direction. (69)
The primary advantage when placing the 4 EASI electrodes is that their placement is more intuitive and based on surface landmarks making correct palpation of intercostal spaces unnecessary. Besides the advantage of easier electrode placement and possible time saving, the EASI lead system is most likely to increase patient comfort due to only 4 chest electrodes, and to interfere less with clinical procedures like resuscitation. A group of paramedics were very enthusiastic about the use of the EASI lead system in the ambulance, finding it easy to use, especially in women because the electrodes could be placed less obtrusively than the standard precordial electrodes. (70)
It is expected that the waveforms of a derived 12-lead ECG, will deviate from the waveforms of a standard 12-lead ECG. (66) However, since correct precordial electrode placement is difficult, especially in stressful situations like the prehospital setting, a prehospital 12-lead ECG recorded by paramedics with limb electrodes positioned on the torso, will also deviate from a standard 12-lead ECG.
Several studies have evaluated the EASI lead system and found it to be equivalent to the ML ECG for detecting arrhythmias, acute ischemia in acute coronary syndrome (ACS) patients, and ST-segment elevation. (71-74) Additionally, in a study of 282 patients Chantad et al. (75) compared the EASI ECG to the standard 12-lead ECG in regards to detection of cardiac rhythm, and changes in the ST-segment, and found no differences. Wehr et al. (76) also showed that the EASI ECG correctly identified or excluded ST-segment elevation when compared to the standard 12-lead ECG in 203 patients. Similar to when limb electrodes are placed in ML positions, a shift in the frontal plane electrical axis is seen with the EASI-derived ECG. (58) However, both types of ECG can potentially be enhanced by improved mathematical transformations. (77)

EASI versus paramedic recorded ECG

Study I is the first study comparing EASI-derived ECG with 12-lead ECG recorded by paramedics. The study showed that the EASI-derived 12-lead ECG and a paramedic obtained 12-lead ECG deviated equally from a standard 12-lead ECG regarding 6 different waveform measures: Q-wave duration, Q-wave amplitude, ST-segment deviation at J-point, R-wave amplitude, T-wave amplitude, and T-prime amplitude. However, our second EASI study showed that the clinical triage decision was influenced, as physicians tended to be more likely to change the level of patient care based on EASI-derived 12-lead ECG compared with 12-lead ECG obtained by paramedics even though no significant differences were seen in waveform morphology. (58) Accordingly, patient care was both upgraded and downgraded based on the occurrence or disappearance of signs of ischemia/infarction in the EASI ECG. It would be of interest to determine the prognostic consequence of this difference in a future study.

The placement of the EASI electrodes by a trained and certified ECG technician in Study I did not allow us to test the diagnostic accuracy of the EASI lead system. Neither was it possible to compare the diagnostic performance of the EASI-derived 12-lead ECG to that of the paramedic 12-lead ECG regarding ST-segment changes, because the ECG was recorded in healthy individuals. As a consequence we performed a second study including acute chest pain patients brought in by ambulance to the ED in Lund (n=20). However, only one of these patients had ST-segment abnormalities defeating the plan to compare acute ST-segment changes in the two types of ECG. We found that EASI-derived 12-lead ECG, and 12-lead ECG obtained by paramedics using the ML limb electrode positions were equivalent regarding Q-wave duration, R-wave amplitude, and ST-segment deviation in chest pain patients. (58)

Our third EASI study was executed during ischemia in patients undergoing PCI.57 These patients had 3 ECG recorded: 1) EASI ECG, 2) ECG with standard precordial electrodes but ML limb electrode positions, and 3) ECG recorded from precordial electrodes placed in clinical practice by paramedics or ED technicians using ML limb electrode positions. ST-segment changes were compared before and after balloon inflation in the 3 ECG. The ability to detect acute ischemia was similar by EASI compared to ECG recorded in clinical practice using ML limb electrode positions confirming prior results. (72-74) Another study has compared real life prehospital ML ECG with prehospital EASI ECG, and showed that the distribution of rhythm, conductions abnormalities, and ST-segment changes were similar for prehospital ML and EASI ECG. (70)

EASI for monitoring

In daily clinical practice, during both ambulance transportation and hospitalization, monitoring is useful for clinical decision support in detecting transient changes such as arrhythmia or ST-segment changes in patients with ACS. For basic purposes as determining heart rate and cardiac rhythm a single bipolar ECG lead of just 2 or 3 electrodes, providing one view of the heart, may be enough. For more sophisticated continuous monitoring, including localization of acute myocardial injury, or distinguishing supra-ventricular versus ventricular origin of wide QRS rhythms, well established standard ECG criteria is needed for an accurate diagnosis. (78;79) Accordingly, continuous 12-lead monitoring is superior in detecting ongoing ischemia (78;80), and predicts outcome more precisely compared to standard monitoring. (81) However, 12-lead monitoring is impractical for the previously mentioned reasons. Since the EASI lead system provides a 12-lead ECG, and is less susceptible to movement artifacts (72;82) it may then be very useful for monitoring purposes including risk stratification.

Conclusions

The standard 12-lead ECG is not suitable for the prehospital setting because it requires accurate precordial electrode placement by careful palpation of bony landmarks, and the distal limb electrodes mandates the patient to be at ease. Consequently, in daily clinical practice precordial electrodes are often misplaced and limb electrodes is moved to ML positions resulting in waveform alterations and possible diagnostic errors.

The EASI lead system is an attractive alternative to the standard ECG because it with easily located 4 chest electrodes possesses several clinical advantages in the prehospital setting, and for ambulatory monitoring purposes. A considerable research effort has been conducted towards evaluation of the EASI lead system. In general the EASI ECG has been shown to produce similar waveforms, and to be equivalent to the standard 12-lead ECG for a wide range of cardiac abnormalities. However, the EASI ECG does, just like ECG recorded from misplaced precordial electrodes, and ML limb electrodes, cause occasional diagnostic errors. Consequently, neither must be considered equivalent to a standard 12-lead ECG.

Even though, theoretically attractive, the EASI lead system has not gained general acceptance in emergency medicine despite enthusiasm among paramedics involved in EASI studies. The reasons for this are probably diverse. First of all, no study has shown the EASI ECG to be superior to ML ECG for diagnostic purposes. Secondly, and perhaps most importantly the standard electrode placements has been well integrated into medical practice for decades with apparently good results. Third, it can be speculated whether paramedics and physicians are aware of the potential for diagnostic errors due to misplaced electrodes. It would probably require a huge effort from the company behind the EASI system (Phillips Healthcare), devoted cardiologists, and paramedics to get the EASI system incorporated into the prehospital setting. For now it seems that the EASI lead system instead has a future within monitoring.

CHAPTER 4

ACCURATE PREHOSPITAL ECG DIAGNOSIS

In order to improve prehospital care, including up-stream diagnosis and treatment in cardiac patients the departmental bill no 1039 from 2000, ordered all ambulances in Denmark to be equipped with defibrillators and a device for 12-lead ECG recording and tele-transmission. (83) Today, prehospital 12-lead ECG acquisition with limb electrodes placed in ML positions has become the standard of care in Denmark as well as many places in the developed world, and ongoing education in 12-lead ECG acquisition, transmission, and interpretation, as well as cardiac pathophysiology, have become an integral part of the training program for ambulance personnel. (83)

In Denmark, the primary ambulances are staffed by emergency medical technicians (EMT). These ambulances are supported by ambulances manned with paramedics, nurses, or physicians depending on the local region's prehospital services. (84) The ambulance personnel is educated in recording and transmitting ECG, while the final diagnosis and triage decision rest upon a cardiologist at one of the 5 tertiary hospitals performing pPCI in Denmark. In contrast, some paramedics in the United States are

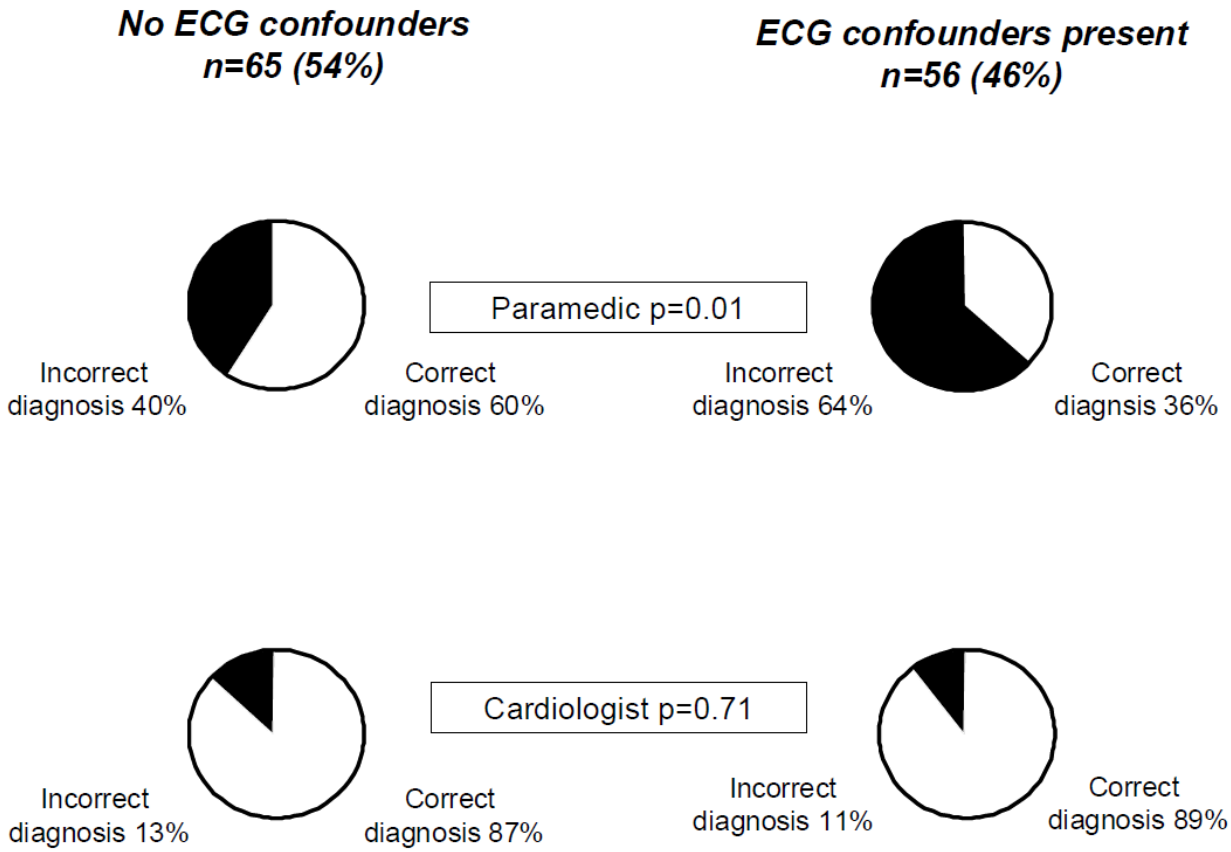

Figure 5
ECG confounders influence on a correct STEMI diagnosis by paramedics and a cardiologist

only to transmit ECG to a cardiologist in patients, they have diagnosed with STEMI (Study II). As a result of this ECG screening prior to transmission, the cardiologist rely on the paramedics for a correct initial diagnosis. Consequently, if the cardiologists are primarily to receive ECG from patients with a high likelihood of

STEMI, then paramedics must be well trained, and experienced in performing and interpreting ECG.

Sensitivity versus specificity
With any diagnostic test there is a tradeoff between sensitivity and specificity. In cases where initiation of prehospital fibrinolysis is an option high specificity is essential to ensure a low risk of treating false positive patients. In such situations, where high specificity is required it may be appropriate to increase the cut-point for ST-segment elevation. In settings where patients are sent for pPCI high specificity is still desirable from a system perspective because of the cost related to activation of the catheterization laboratory, but it would be appropriate to accept a lower specificity in trade for a higher sensitivity for STEMI classification to ensure early treatment in all patients presenting with STEMI.

Paramedic versus cardiologist diagnosis of STEMI
The purpose of Study II was to determine paramedics' ability to diagnose STEMI in the ambulance in one county in North Carolina, USA, and to assess the influence of ECG confounding factors on the paramedics' diagnosis. Paramedics were instructed in diagnosing STEMI in cases of ST-segment elevation of more than 1 mm in at least 2 contiguous leads. A final diagnosis of STEMI was then determined by acute coronary angiography and/or evolution in serial ECG accompanied by a transient increase in creatine kinase myocardial band (CKMB). ECG confounding factors included: LBBB, RBBB, left anterior/posterior fascicular block, left/right ventricular hypertrophy (LVH/RVH), ventricular rhythm, Wolff-Parkinson-White syndrome, Brugada syndrome, poor quality ECG e.g. unstable baseline and lead reversal, prior MI with persistent ST-segment elevation, benign early repolarisation, intraventricular conduction abnormalities, acute pericarditis, ischemic dilated cardiomypatia, left ventricular aneurism, and pacemaker rhythm. (3;85) Study II showed that the paramedics' overall positive predictive value (PPV) of STEMI based on the initial prehospital ECG was 60% in patients without ECG confounding factors, while the presence of particularly LBBB, prior MI, or LVH lowered the paramedics PPV to 36%. In contrast, the cardiologist's overall PPV of 88% for diagnosing STEMI was not influenced by the presence of confounding factors (figure 5). This difference in the ability to diagnose STEMI correctly is not surprising given that cardiologists must be considered specialists in ECG interpretation, while paramedics have several other medical fields they operate within. However, if paramedics are to screen ECG for the presence of STEMI, then they must be trained in recognizing the most common confounding factors that mimic or mask ACS.
As a consequence of Study II paramedics in Guilford County, NC, USA received additional training in ECG diagnostic and may now activate the catheterization laboratory when they diagnose STEMI in ECG without confounding factors. In cases with an ECG con-

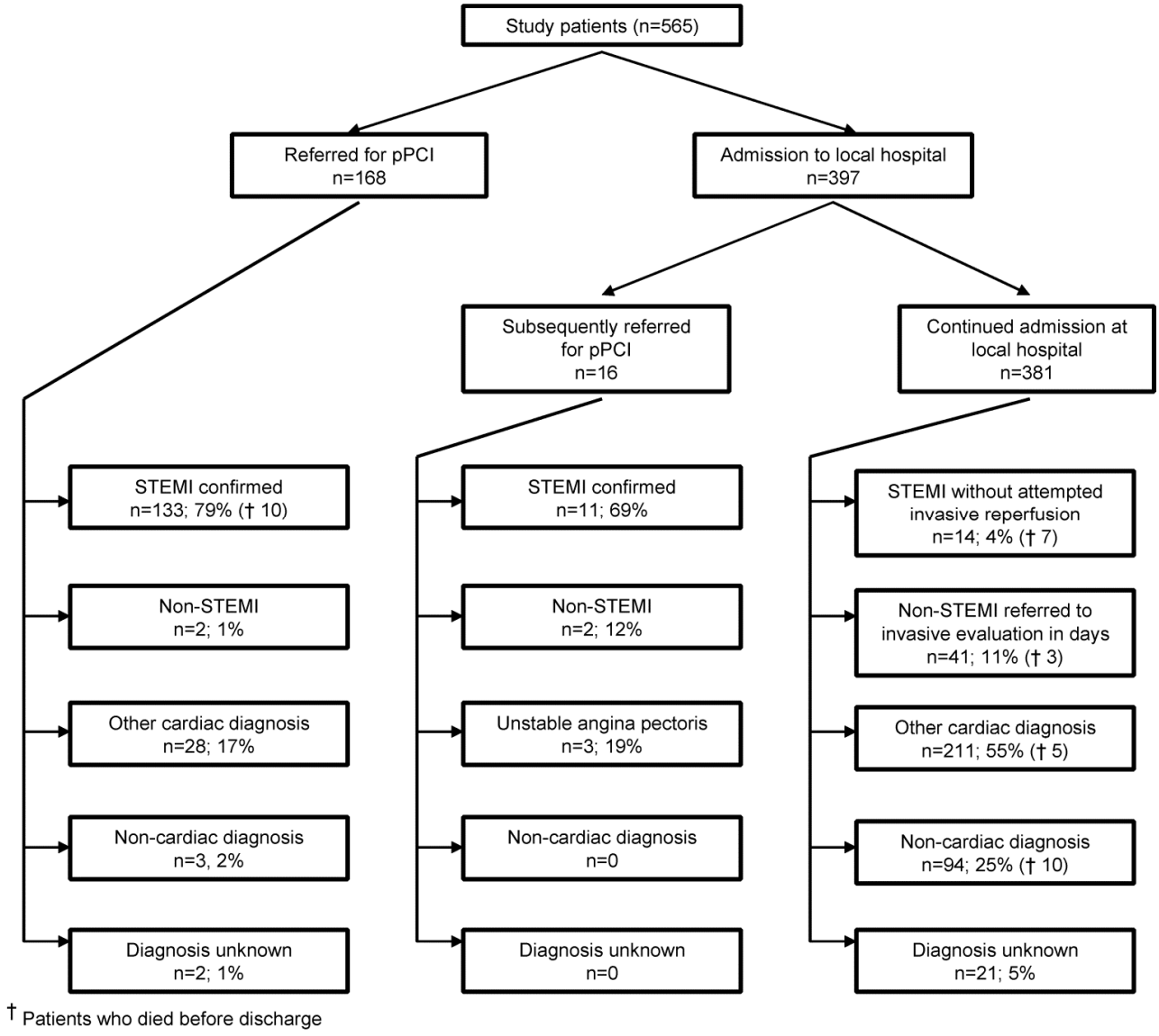

Figure 6
Triage based on transmission of prehospital ECG to a cardiologist, and final hospital diagnosis in patients presenting with chest pain in Study III. pPCI: Primary percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction
Reprinted from Sejersten et al. Am J Cardiol 2008;101:941-946. With permission from Elsevier.

founder, the ECG is transmitted to the ED, and the ED physician makes the decision of whether to activate the catheterization laboratory or not (personal communication). A follow-up study to determine whether the paramedics achieve a higher PPV after implementation of the current set-up is being planned.
In a study including 151 patients with high clinical suspicion of STEMI paramedics were instructed to identify STEMI patients with high specificity and thereby minimize the false positive rate of STEMI. (86) The paramedics sensitivity was 80% and specificity 97% (PPV 83%, NPV 96%), and comparable to the results achieved by an emergency physician and a cardiologist. Based on these results the authors suggested that ECG transmission to a cardiologist is unnecessary. However, the results should be evaluated with care because the study did not include all patients with chest pain, and excluded patients with LBBB and pacemaker. The paramedics' high false positive rate of STEMI in Study II may have been caused by a tendency to "over-diagnose" rather than "under-diagnose" to secure early patient care and to shorten time to reperfusion therapy. However, this approach may put patients in danger of receiving potentially dangerous therapies and procedures. Accordingly, misinter¬pretation of ECG may significantly impact medical care such as unjustified thrombolytic therapy and consequently increase the occurrence of adverse outcomes. (87;88)
A limitation to Study II is that only data from patients that the paramedics classified with STEMI was available. It was not possible to collect data from patients that the paramedics classified not to suffer from STEMI because many were discharged directly from the ED with no further ECG recordings, enzyme values, or angiography. Consequently, the numbers of false and true negatives in Study II are not known.

ST-segment elevation and STEMI

In 912 consecutive chest pain patients with a prehospital ECG transmitted to a cardiologist for triage at our institution 40% had ST-segment elevation, and 73% of these had STEMI according to the discharge diagnosis. The majority (89%) of patients with ST-segment elevation, but not STEMI, had a conduction defect, ventricular hypertrophy, or a small or old MI causing the ST-segment changes (personnel communication). In another study of 902 chest pain patients only 22% had ST-segment elevation, and only 15% of these had a final discharge diagnosis of STEMI. (85) The confounding factors LVH, LBBB, and benign early repolarization accounted for the majority of the cases with ST-segment elevation but not STEMI. (85) Jet another study confirmed that LVH and LBBB most frequently caused ST-segment elevation in the absence of STEMI. (89) Consequently, ST-segment elevation alone lacks the PPV necessary for reliable prehospital STEMI diagnosis. By inclusion of reciprocal ECG changes the PPV of prehospital AMI criteria increased to more than 90%, suggesting that ST-segment elevation criteria in combination with reciprocal changes can identify patients most likely to benefit from early interventional strategies. (89) Similarly, Martin et al. (90) found that consideration of both ST-segment elevation and depression significantly increased the sensitivity from 50% to 84% for detection of STEMI with only a slight decrease in specificity from 97% to 93%.

Triage of chest pain patients

Real life triage of chest pain patients by a cardiologist based on prehospital ECG transmission in Study III showed that 87% of 168 patients referred for pPCI received immediate catheterization (pPCI 80%, angiography only 19%, and emergent bypass surgery 1%). Of patients not receiving intervention 8 died before pPCI, 1 declined invasive treatment, and 8 were re-evaluated upon hospital arrival and had no indication for pPCI. STEMI was confirmed in 79% (n=133) of patients referred directly for pPCI. In comparison, STEMI was found in 6% (n=25) of patients admitted at local hospitals after a cardiologist had judged them not to have STEMI (Figure 6). Study III was not designed to determine the cardiologist ability to diagnose STEMI, but the results remain interesting showing that the PPV and NPV for diagnosing STEMI for trained cardiologists were 79% and 94%, respectively (sensitivity 84%; specificity 91%).

A wide variation even among experienced "electrocardiographers" in differentiating STEMI with the need for pPCI from other conditions causing ST-segment elevation has been shown in a study including 116 ECG with ST-segment elevation of which only 7% were STEMI. (91) In this study the PPV ranged from 18-67% and the NPV from 96-100% (sensitivity: 50-100%; specificity: 73-97%). However, this population was very different from the populations in Study II and Study III where respectively 49% and 28% of patients suffered from STEMI.

Identification of certain electrocardiographic confounders

Zhou et al. (92) have developed and optimized an algorithm to help distinguish between STEMI, benign early repolarization, and acute pericarditis. Employment of such an algorithm may assist paramedics in differentiating among these three conditions. As a general rule it has been shown that in STEMI ST-segment elevation is localized to a portion of the ECG leads, and is often accompanied by ST-segment depression in other leads. In contrary, ST-segment elevation in acute pericarditis is diffuse with minimal difference between minimal and maximal amplitudes. Diffuse ST-segment elevation is also seen in benign early repolarization, but the amplitudes are higher in all leads except in lead V1 and III. Tall T-wave amplitudes in all leads but V1 and III are also significant for benign early repolarization when compared to acute pericarditis and early AMI. (92)

Prior studies have shown that 7-23% of all patients with AMI have RBBB or LBBB. (93) In Study II 8.5% of patients with confirmed STEMI had RBBB or LBBB. The presence of LBBB may hide the traditional changes of STEMI, and without a previous ECG it can be very difficult to determine if a patient with chest pain has STEMI. Consequently, these patients are often treated insufficiently with both delayed diagnosis and treatment. (94) LBBB was one of the confounders that caused the paramedics difficulties in Study II. Sgarbossa et al. (95) have proposed 3 electrocardiographic criteria with high specificity but low sensitivity for diagnosing STEMI in patients with LBBB. The criteria are: 1) ST-segment elevation of ≥1 mm concordant with the QRS complex; 2) ST-segment depression of ≥1 mm in lead V1, V2 or V3; and 3) ST-segment elevation of ≥5 mm discordant with the QRS complex. However, subsequent studies (96;97) have found an ever lower sensitivity, why the criteria can only be of assistance for paramedics when ruling in STEMI, but not ruling it out.

Electronic assistance in diagnosing STEMI

Automated ECG interpretations based on computerized algorithms have been developed to improve the sensitivity and specificity of prehospital 12-lead ECG diagnosis. (98) Computerized ECG interpretation programs must have a high specificity in order to minimize the possibility of treating inappropriate patients. However, at the same time the program must demonstrate high sensitivity in order to rapid detect patients with very early AMI. Most algorithms have been developed in non-acute settings. Consequently, the algorithms sensitivity may be too high for the prehospital setting, because high sensitive criteria increase the number of falsely abnormal ECG. Van't Hof et al. (99) showed that paramedics with the help of a computerized electro-cardiographic algorithm had a 95% PPV for diagnosing STEMI correctly. In comparison the PPV rose to 99% in patients diagnosed and triaged for pPCI at a local referral hospital. Computerized ECG interpretations and a cardiologist diagnosis have been shown equally reliable in one study (100), while another have shown that computer interpretations were less sensitive compared to a cardiologist's review for diagnosing various conditions including anterior and inferior AMI, LVH and RVH. (101) Advantages and disadvantages by paramedic interpretation, computerized ECG interpretations, and wireless transmission to a physician are listed in Table 1.

Conclusions

With the recommendation of recording prehospital ECG by EMS in all patients with symptoms suggestive of ACS it is pivotal that the acquired information is effectively translated into action. When an early prehospital diagnosis of STEMI is established the EMS personnel may behave with more urgency enhancing quality of patient care and treatment. Study II showed how the presence of ECG confounders influenced a group of trained paramedics in diagnosing STEMI correctly. In ECG without confounding factors their PPV was 60% but dropped to 36% in the presence of confounders. In comparison, the participating cardiologist's ability to diagnose STEMI was almost 90% and not affected by ECG confounding factors. The study emphasizes the need for continued education of ambulance personnel in 12-lead ECG interpretation, especially if they are to screen for patients likely to suffer from

Table 1. Models for interpreting prehospital electrocardiograms

Prehospital ECG interpretation by:	Advantages	Disadvantages
Paramedics	Quick and simple	Continual education and quality assurance is required
	Wireless network and complex technology is not required	Challenging in areas with multiple EMS provides
Computer algorithms	Quick and simple	False-positive and false-negative rates higher than physician interpretation
	Wireless network and complex technology is not required	
Physicians (by wireless transmission)	Early contact with a physician with decision making power for: triage, activation of the catheterization laboratory, and initiating prehospital therapy	New technology is required for EMS providers and hospitals
		Wireless network and transmission unit on ambulances must be reliable
	Theoretically lowest rate of false-positives and false-negatives	A system must ensure immediate interpretation by physician
		Transmission failures

ECG: Electrocardiogram; EMS: Emergency medical services; PDA: Personal digital assistant

STEMI, and transmit only abnormal ECG to the attending cardiologist, or if ECG transmission is not an option and paramedics are responsible for triage and initiating treatment.
In a "real life" clinical setting with ECG transmission to a cardiologist for triage decisions we found that the cardiologists' PPV and NPV for diagnosing STEMI were 79% and 94% respectively. It would be of future interest to investigate if this could be optimized using computer algorithms and/or online ECG archives with previous patient ECG to support cardiologists in the triage decision.

PREHOSPITAL ECG TRANSMISSION FOR EARLY DIAGNOSIS AND TRIAGE

The technology of cellular telephonic transmission of prehospital 12-lead ECGs from the ambulance to hospital receiving stations has been available for more than 20 years. (102) Currently wireless transmission systems for recording prehospital ECG are commercially available from 4 companies: Phillips Healthcare (Andover, Mass, USA), Physio-Control Inc. (Redmond, Wa, USA); Ortivus (Danderyd, Sweden), and Zoll Medical (Chelmsford, Mass, USA). The number of ambulances carrying equipment to record and transmit 12-lead ECG is increasing, with more than 1/3 of all ambulances possessing this ability in Europe and the Unites States. (103) The technology allows remote diagnosis and facilitates early triage of patients with STEMI to reperfusion therapy, and initiation of adjunctive therapies already in the prehospital setting. Additionally, the receiving hospital attains early notification of incoming patients, and can prepare for either immediate hospital fibrinolysis or activate the catheterization laboratory. Several studies have demonstrated a reduction in time to reperfusion therapy with rapid ECG availability. (104-109) Terkelsen et al. (104) found that time to thrombolysis was significantly reduced in patients with the STEMI diagnosis established in the ambulance versus in hospital (38 vs. 81 minutes). By prehospital ECG transmission to the emergency department Wall et al. (105) documented a 27% (109 min to 80 min) reduction in time from EMS arrival at the hospital to successful implementation of pPCI. However, transmission of ECG to a receiving station within hospitals requires that the physician on-call is in close proximity of the

Table 2 Prehospital delays for study patients and DANAMI-2 controls

Times	Study patients (n=565)	DANAMI-2 (n=89)	P-value*	Local hospital (n=397)	Referred (n=168)	P-value†
Patient delay	37 (11-96)	64 (20-166)	<0.001	51 (11-123)	31 (8-66)	0.02
Ambulance response time‡	6 (4-7)	-	-	6 (4-8)	6 (4-7)	0.9
Prehospital ECG timing‡	11 (7-16)	-	-	12 (7-16)	10 (7-14)	0.06
Ambulance on-scene time‡	22 (18-27)	-	-	22 (18-27)	22 (17-27)	0.9
Ambulance departure-to-Door	11 (8-18)	85 (65-115)§	<0.001	10 (6-15)	12 (9-20)	<0.001
911 call-to-Door	39 (32-47)	103 (76-133)	<0.001	38 (32-44)	41 (32-49)	0.08
Electrocardiogram-to-Door	23 (16-30)	60 (48-80)	<0.001	20 (14-25)	24 (16-32)	0.001

Times are median minutes (interquartile range)
* Study patients versus DANAMI-2 controls.
† Patients admitted to local hospitals versus referred patients.
‡ Scene arrival time was not available in DANAMI-2.
§ Includes transport to a local hospital for ECG recording, establishment of the diagnosis, and transport to a tertiary center for primary percutaneous coronary intervention.
ECG: electrocardiogram
Modified from Sejersten et al. Am J Cardiol 2008;101:941-6. With permission from Elsevier.

receiving station to quickly view and interpret the ECG to ensure an early triage decision. Transmission to a receiving station in the ED may also require cardiology consultations on arrival, which can create further delays. (110) A solution would be to transmit the ECG directly to the cardiologist's phone or handheld computer (Study III). (111;112) With transmission to a handheld device the cardiologist would be available for a consultation including ECG analysis even if located remote to the receiving station within or outside the hospital. The large advantage of this technology is the direct contact with an ECG specialist with real decision-making competence and the ability to activate the catheterization laboratory. With the cardiologist's expertise it may also be possible to reduce the number of times the catheterization laboratory team is falsely activated due to an incorrect diagnosis. Receiving transmitted ECG in all patients with chest pain, unexplained shortness of breath, or resuscitated cardiac arrest will increase the attending cardiologists' work burden. However, it also allows the cardiologist to prepare and plan ahead for incoming patients. In 912 consecutively transmitted ECG to our institution 29% were positive for STEMI. The in-hospital on-call cardiologists did not find it to be a problem to receive 2-3 negative ECG for every STEMI patient they send to pPCI (personal communication). In places where cardiologists are on-call outside the hospital and does not tolerate a large number of incoming ECG, appropriate education of the ambulance personnel, and use of automated diagnostic statements may improve prehospital ACS screening so only abnormal ECG are transmitted to the cardiologist on-call.

Prehospital ECG transmission

The feasibility of transmitting a prehospital 12-lead ECG directly to a handheld device carried by a cardiologist for confirmation of STEMI and early notification and assembly of the catheterization laboratory team before patient arrival had not previously been investigated when Study III was planed and initiated in urban Copenhagen. It was hypothesized that this system would reduce time to pPCI when patients diagnosed with STEMI based on the prehospital 12-lead ECG were transferred directly to the catheterization laboratory bypassing local hospitals and the ED.
Prior to initiation of Study III, ambulances had been equipped with a LIFEPAK 12 (Physio-Control. Inc., Redmond, Wa, USA) monitor/defibrillator capable of transmitting 12-lead ECG via the global system for mobile communication (GSM) network. Ambulance personnel had been educated in correct procedures for recording and transmitting 12-lead ECG. They placed precordial electrodes in standard positions as accurately as possible, while limb electrodes were placed according to the ML positions. In ambulances manned with a physician the ECG was screened and only abnormal ECG was transmitted, while ambulances manned with EMT and paramedics transmitted all recorded ECG.
The prehospital 12-lead ECG was transmitted from the ambulance to a receiving station located in the CCU, where it was stored, displayed and printed. Simultaneously, the ECG was forwarded to the on-call cardiologist's mobile phone (Nokia 9210, Nokia group, Finland) (Figure 7). The cardiologist could view all 12 leads, 6 leads, or zoom in and view one lead at the time. A 1 mm grid made it possible to accurately determine the amount of ST-segment deviation in all leads. Viewing an ECG on a sheet of paper versus on a liquid crystal display (LCD) screen is somewhat different, but two previous studies have shown that the LCD ECG can be reliably interpreted, and cardiologists' diagnostic decisions are similar when viewing traditional paper ECG versus LCD ECG. (113;114) A second phone was used to communicate the patient's clinical condition. Based on the ECG and clinical information the cardiologist made the triage decision of whether the patient should be transferred directly to the catheterization laboratory or admitted at a local hospital. A total of 565 patients were included in Study III from October 2003 to October 2005.

ECG transmission success and quality

During the calendar year preceding Study III a pilot study was carried out, with the purpose to recognize flaws in the system and

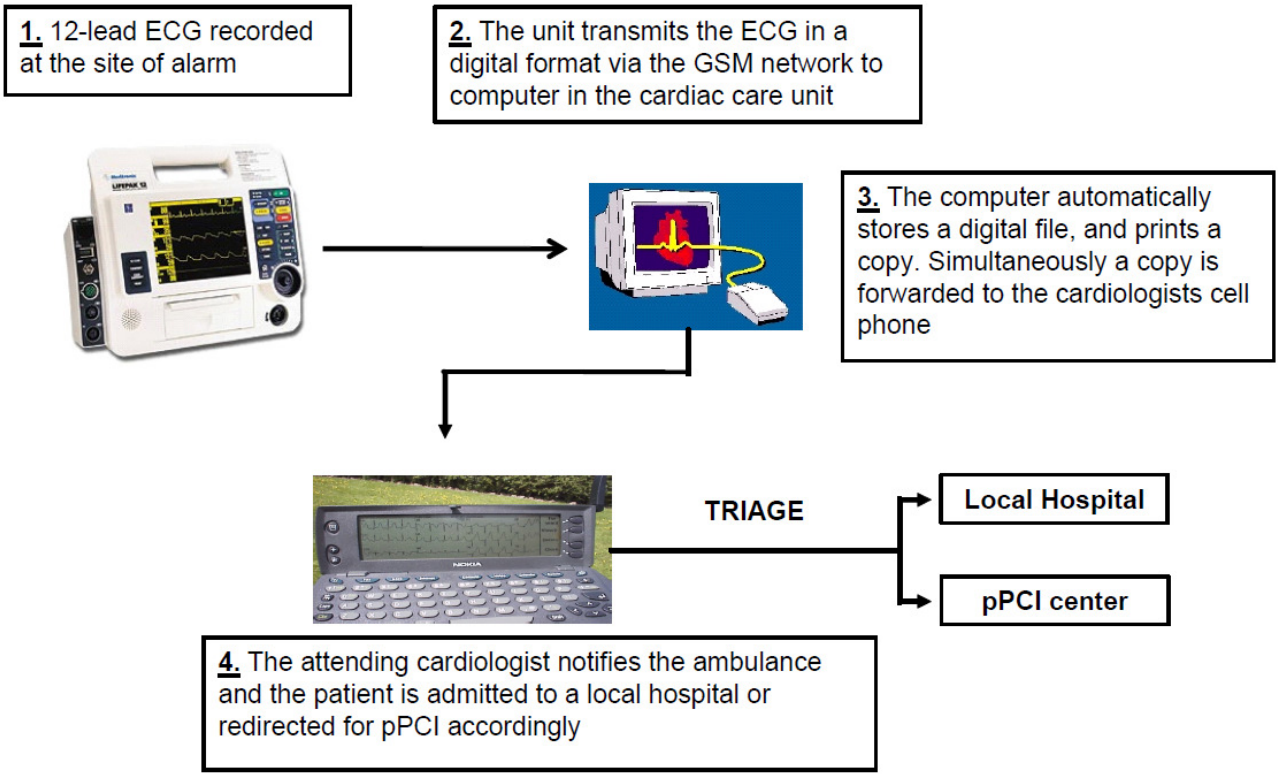

Figure 7
Set-up for prehospital 12-lead electrocardiogram transmission in Copenhagen. ECG: electrocardiogram; GSM: Global system for mobile communication; pPCI: Primary percutaneous coronary intervention.

correct them prior to initiation of the main study. (115;116) The successful ECG transmission rate during this first year was 89%, but rose to 94% during Study III. The reasons for transmission errors in Study III were unknown in almost 1/3 of cases, with different technical issues responsible for the remainder of the unsuccessful transmissions. Noteworthy, human errors, including negligence to carry the phone, or recharge the batteries, were only registered during the pilot phase.
In a study by Terkelsen et al. (104) unsuccessful transmissions was seen in 14% of cases and the causes were: geographical setting (7%), lack of patient cooperation (5%), and technical problems (2%). Increased acquaintance to the system, technical developments, widespread and dependent GSM networks, and further optimization of standard operating procedures may increase the transmission success rate.
The ECG quality depends on several variables including: where the ECG is recorded (on scene, in the ambulance, during transport), the patient's condition (calm, agitated), the placement of both precordial and limb electrodes, the equipment, and the expertise of the person recording the ECG. The quality of the transmitted ECG was not assessed in Study III, but in Study II approximately 10% of ECGs recorded by well-trained American paramedics were characterized as poor quality due to unstable baseline or electrode reversal. Other studies have shown a higher quality of prehospital ECG. Kudenchuk et al. (117) found that 99.7% of the prehospitally recorded ECG were suitable for diagnostic purposes. Similar findings were reported by Terkelsen et al. (104) where the technical quality of the transmitted ECG was good in 78% (average in 20%, poor in 2%), and technically acceptable for diagnostic purposes in 98% of cases.

Prehospital delays
Delay in initiation of reperfusion therapy is a tremendous problem in the treatment of STEMI patients. The reasons are many and every step from symptom onset to reperfusion can potentially delay treatment. In the DANAMI-2 study prehospital delay was median 105 minutes, while patients randomized for pPCI and admitted at a local hospital before transfer to a tertiary pPCI hospital spend an additional 50 minutes at the local hospital before transfer, awaiting a 12-lead ECG to be recorded, and a physician escort. (42) The National registry of myocardial infarction (NRMI) (118) showed that only 4% of patients with inter-hospital transfer for pPCI obtained a door-to-balloon time within 90 minutes from arrival at first hospital. A way to ensure more frequent and earlier reperfusion therapy, and even reduce short-term mortality, is bypassing the receiving hospital ED. (119)
Table 2 lists prehospital delays seen in Study III. Patient delay of 37 minutes is low compared to the 60 minutes observed in a prior Danish study with 153 patients admitted for suspected ACS. (120) The low patient delay is a surprising finding since Denmark has not had any recent national campaigns to educate the public to seek medical assistance in case of chest pain. On the other hand, national campaigns elsewhere have failed to produce long-term effects in reducing patient delay. (121) The short patient delay may then be a chance finding given the small numbers, but it may also be caused by a general increase in the awareness of ischemic heart disease in the population, and the major news effect following the change in the recommended treatment strategy in STEMI patients after DANAMI-2.

Table 3 Delays in patients receiving emergent catheterization after direct referral versus DANAMI-2 controls

Times	Referred (n=146)	DANAMI-2 (n=89)	p-value*	pPCI - center #1 (n=101)	pPCI - center #2 (n=45)	p-value†
911 call-to-pPCI	74 (64-94)	127 (103-151)	<0.001	73 (62-93)	82 (64-97)	0.24
‡Electrocardiogram-to-pPCI	57 (49-75)	83 (68-107)	<0.001	63 (46-75)	56 (50-80)	0.99
§Door-to-pPCI	34 (19-46)	97 (80-124)	<0.001	35 (27-50)	20 (13-38)	0.003
§Door-to-balloon	49 (32-64)	112 (92-143)	<0.001	57 (45-65)	40 (28-55)	0.003

Times are median minutes (interquartile range)
*Referred patients versus DANAMI-2 controls.
†Referred patients at primary percutaneous coronary intervention center #1 versus center #2.
‡ The first electrocardiogram was recorded after arrival at the randomization hospital in DANAMI-2
§ Door defined as time of arrival at first hospital.
pPCI: primary percutaneous coronary intervention
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The significantly shorter patient delay for patients referred for pPCI compared to patients admitted to a local hospital following the cardiologists triage decision in Study III may reflect that these patients are at higher risk. This is supported by previous studies in where early presenters had the largest ST-segment elevation (118), and highest risk score at presentation. (122) A relationship between time of presentation and amount of ST-segment elevation is also seen in Study V. This finding supports the assumption that patients with most ST-segment elevation have a larger amount of jeopardized myocardium and thus greater discomfort urging them to seek medical help sooner than patients with less myocardial involvement. In conjunction with this reasoning, patients with poor left ventricular function and high mortality risk have shown a tendency to seek medical help soon after symptom onset. (123;124) Accordingly, in the era before reperfusion therapy Löwel et al. (125) found that early presenters (<1h) had the highest mortality rate compared with patients presenting the following 23 hours.

Ambulance response time of 6 minutes was low reflecting the urban setting of Study III. Since the 12-lead ECG represents the critical data for diagnosis and decision making in chest pain patients it should be prioritized and performed as early as possible. The 11 minutes from ambulance arrival to ECG recording in our study is acceptable, but increased awareness of the relationship between time delay and outcome in STEMI may urge the ambulance personnel to record an ECG even earlier. Scene time in Study III of 22 minutes corresponds well with prior studies reporting times of 14 to 26 minutes. (126;127) The pilot study preceding Study III (115;116) showed that median time spent at the scene rose by 7 minutes after the implementation of prehospital ECG recording. Other studies have shown a 2-5 minute increase in scene time after implementation of prehospital ECG recording. (128;129) Canto et al. (106) suggested that it is not the recording of the prehospital ECG alone that increases scene time, but other initiatives contribute e.g. intravenous catheters, and administration of medication. However, the increased scene time may be reduced with acquaintance to the system, more experienced ambulance personnel, and increased focus on the crucial impact on patient outcome by establishing an early diagnosis. The increased scene time is compensated by an early notice of the receiving hospital, allowing preparation for patient arrival. Accordingly, in the NRMI-4 door-to-fibrinolysis and door-to-balloon was significantly shorter in patients with a prehospital ECG. (130)

Hospital delays

The design in Study III with implementation of a STEMI network with referral of STEMI patients directly to pPCI based on transmission of prehospital 12-lead ECG to the attending cardiologist reduced door-to-PCI from 97 minutes to only 34 minutes (Table 3). The use of a historical control group for this comparison was not optimal. However, since ECG transmission had already shown to reduce time to pPCI (105), and all ambulances in the area had the capabilities of ECG recording and transmission, it would have been unethical not to record and transmit prehospital ECG in all patients.

Time to treatment in many hospitals (118) does not meet international guidelines stating that pPCI should be initiated within 90 minutes of first medical contact (48;49), and as a consequence mortality rates may increase (32;131) When prehospital ECG lead to activation of the catheterization laboratory the portion of patients with a door-to-balloon time within 90 minutes increased from 33% to 55%. (130) A further increase was seen in Study III, with 98% of patients obtaining a door-to-PCI time within 90 minutes. This is remarkable given the short transportation time, and thus the limited time to activate the catheterization laboratory prior to patient arrival.

Two small studies have shown similar time savings by transmitting the ECG directly to a cardiologist's handheld device. (112;132) The study by Adams et al. (132) used more complex transmission procedures requiring accurate interpretation of STEMI by the paramedics, notification of an ED nurse of the incoming ECG, manual conversion of the ECG to another format, and manual forwarding to an e-mail address before the ECG was accessible to the cardiologist. This design is less attractive than the one used in both Study III and the study by Dhruva et al. (112), where the ECG was received on the cardiologist's handheld devise automately once it had been transmitted from the ambulance.

Door-to-PCI times increased significantly from 20 minutes to 37 minutes during off-hours (4 p.m. – 8 a.m.) with the catheterization team being on-call from home and a maximum respond time of 30 minutes (Study III). A previous study has shown similar delays in treatment times during off-hours. (133) In order to reduce time to treatment during off-hours the catheterization team may need to stay at the hospital increasing the cost of the procedure.

Scholz et al. (134) showed that a formalized data feedback system impressivly reduced door-to-ballon time from 54 minutes to 26 minutes. For every 3 months an interactive session with all stakeholders involved in the STEMI network was conducted. Data collected during the preceding quarter(s) were presented and discussed in detail to identify any steps that could cause treatment delays. A feedback system like this may improve the processes in two ways. First of all by increasing each individuals understanding and acceptance of his or her role in the process, and secondly by creating a sense of individual and team accountability. With the implementation of a formal data feedback system the times observed in Study III may be condensed even more.

Outcome

Follow-up data were not available in Study III, and therefore it was not possible to determine whether the reduced time to treatment had an effect on mortality. However, with prior studies (32;131) showing a strong relationship between time to treatment and mortality it may be assumed that the observed 1 hour reduction in time to pPCI would reduce mortality.

Interestingly, Study III showed no difference in in-hospital mortality between patients redirected for PCI and patients admitted to a local hospital. The vast majority of deaths (≈70%) in patients admitted at local hospitals were cardiac. All chest pain patients should therefore receive special attention and undergo rhythm monitoring and serial ECG recordings at the local hospital. The ECG recordings/ monitoring should be used to identify STEMI equivalents, discrete occlusions not meeting STEMI criteria, and determine infarct size for initiation of relevant therapy. Even early angiography may be a necessary step to identify patients with 3 vessel disease or left main coronary occlusion in need for CABG.

Conclusions

Prompt reperfusion is crucial for survival in STEMI patients. A host of strategies have therefore been initiated in the pursuit to minimize delay in every step from symptom onset to initiation of reperfusion therapy. The initiative of prehospital ECG recording followed by transmission to receiving stations in hospitals has been associated with a significant reduction in treatment delay. Study III showed that prehospital ECG transmission directly to a cardiologist's handheld device for diagnosis and early triage significantly reduced time to treatment in STEMI patients, and ensured reperfusion therapy within guideline recommendations. The impressive reduction in treatment time may be ascribed to a combination of early diagnosis, the cardiologist's decision making power to activate the catheterization laboratory, and direct patient transport to the catheterization laboratory without delays in the ED or CCU.

The delay accompanied by long distances between patients and tertiary pPCI hospitals are hard to overcome if transport is manned to be by ambulance. Future studies are needed to determine if time can be further reduced if patients with long transport distances are flown by helicopter versus transported by ambulance.

CHAPTER 5

THE ECG AS DECISION SUPPORT FOR CHOICE OF REPERFUSION THERAPY

With the ECG being a non-invasive and inexpensive tool ready available at bedside it would be most favorable if the initial ECG could reveal information that would help the clinician to tailor the most optimal treatment strategy for the individual patient. Maybe the ECG can help identify patients who will benefit greatly from reperfusion therapy versus patients with modest effect. Additionally, the ECG may identify patients who will have a better prognosis with pPCI versus patients who will obtain similar outcome with fibrinolysis. Accordingly, costs of pPCI could be saved and some patients protected from the stress of being sent to a distant hospital for an acute intervention.

ANDERSON-WILKINS ELECTROCARDIOGRAPHIC ACUTENESS SCORE

Currently, time from symptom onset in STEMI patients is used for choosing the optimal treatment strategy, since the potential for survival after reperfusion therapy is reduced over time and not apparent 12 hours after symptom onset. (31;32) Accordingly, patients presenting more than 12 hours after symptom onset are often treated conservatively. However, the presence of unspecific symptoms, varying degrees of chest pain, and inaccurate recollection makes it difficult to determine the exact duration of coronary artery occlusion, and thereby the duration of myocardial ischemia in patients experiencing STEMI. The decision of whether to initiate reperfusion treatment may then be based on uncertain subjective estimations of the duration of ischemia. Furthermore, the time course of occlusion may occur abruptly or gradually over several hours. Consequently, a more objective way to determine ischemic time would be preferable to help tailor therapy in ACS.

A prior study has shown that 70-90% of myocardial ischemic episodes detected by ECG (transient ST-segment shift ≥1 mm) are clinical silent, making ECG monitoring more sensitive than patient reported symptoms of chest pain or discomfort for detecting transient myocardial ischemia. (135) Anderson (136), Wilkins (137), and co-workers developed an ECG method for quantifying the acuteness of an evolving AMI (AW acuteness score). The foundation for developing such a method was the serial ECG waveform changes seen in the different phases during acute coronary occlusion: 1) Tall T-waves as a sign of early ischemic myocardium that potentially can be salvaged upon reperfusion; 2) ST-segment elevation demonstrating presence, location, and extent of ischemia, and 3) Abnormal Q-waves as a sign of necrotic myocardium with no ability to achieve salvage.

The AW acuteness score considers all leads in the standard 12-lead ECG (except aVR) with ≥0.1 mV of ST-segment elevation and/or tall T-waves. Each lead is assigned an acuteness phase depending on the presence or absence of tall T-waves as described by Gambill et al. (138) or abnormal Q-waves according to the Selvester QRS score (139) (Table 4). The earliest phase is assigned 1A, followed by 1B, 2A and the latest phase 2B. Four points is allocated for phase 1A, 3 for 1B, 2 for 2A and 1 for 2B. The AW acuteness score range from 1.0 (late/least acute) to 4.0 (early/most acute), and is calculated by the following formula:

$$\frac{4(\#\text{ leads 1A}) + 3(\#\text{ leads 1B}) + 2(\#\text{ leads 2A}) + 1(\#\text{ leads 2B})}{\text{Total \# leads with 1A, 1B, 2A, or 2B}}$$

By incorporating the number of leads with ST-segment elevation and/or tall T-waves the AW acuteness score only reflects timing of the coronary occlusion, and not the anatomic extent of the infarction process.

AW acuteness score calculation is time consuming, and the algorithm must be integrating into commercial automated ECG analysis programs to achieve practical use for clinical decision support in patients presenting with STEMI. (140)

Table 4 Algorithm for designating an acuteness phase of an evolving acute myocardial infarction in each electrocardiographic lead

Phase	Elevated ST	T-wave	Abnormal Q-wave	Score	Acuteness of an evolving AMI
1A	+ or -	TT	-	4	Most acute/early
1B	+	PT	-	3	
2A	+ or -	TT	+	2	↓
2B	+	PT/EN	+	1	Least acute/late

AMI: Acute myocardium infarction
EN: End of T-wave negative
PT: Positive T-wave
TT: Tall T-wave
+: present
-: not present

AW acuteness score versus historical timing

Corey et al. (141) was the first to evaluate the AW acuteness score and found an inverse relationship for both historical timing (patient informed symptom duration) and AW acuteness score versus infarct size determined by SPECT. They concluded that the combination of historical timing and AW acuteness score had complementary value, and provided a more accurate indication of the potential for myocardial salvage, than historical timing alone.
Study IV included 175 DANAMI-2 patients suffering from an anterior myocardial infarction, and showed that the amount of myocardial salvage depended on the AW acuteness score (ECG timing) and not historical timing. Accordingly, patients who were early by AW acuteness score had significant more myocardial salvage after reperfusion therapy compared to patients who were late by AW acuteness score. The association between AW acuteness score and salvage was evident regardless of reperfusion strategy (fibrinolysis versus pPCI) confirming that time to treatment is not only of importance in patients treated with fibrinolysis but also in pPCI.
By combining AW acuteness score and historical timing a small group of patients who were early by historical timing but late by ECG were identified in Study IV. These patients would be expected to have a large potential for salvage due to the short historical timing, but instead they had no salvage after reperfusion therapy. Consequently, post-reperfusion therapy should be prioritized in this group of patients. Concurrently, patients with long historical timing would be expected to have a low potential for myocardial salvage, however if they were early by ECG then salvage was high (Study IV) and infarct size limited. (141)
Study IV is the first to address the prognostic value of the AW acuteness score. The initial increase in salvage in patients early by ECG resulted in reduced 1-year mortality. However this difference in mortality was based on a difference in 10 events, so the results need confirmation in a larger study.
In contrast to mortality, reinfarction rate was not influenced by AW acuteness score. Predictors of reinfarction have been ascribed to variables like age, diabetes, previous stroke, hypertension, multivessel disease, and target vessel diameter. (142) Additionally, Study VII showed a relationship between complete ST-segment resolution and reinfarction in fibrinolyzed patients (see page 25).
A limitation of the AW acuteness score is that it was developed in ECGs without confounding factors and therefore is only valid in the absence of confounders, which may eliminate the score's use in approximately 25% of patients, as seen in Study IV. Only patients with anterior infarcts was included in Study IV since the scoring system had only been validated for anterior infarction. Accordingly, Corey et al. (141) found that the AW acuteness score and historical timing predicted infarct size less accurately in inferior infarcts versus anterior infarcts. The reason for less accuracy in inferior infarcts may be that the standard ECG covers the inferior area with less leads. A solution may be the addition of both aVR and ST-segment depression in leads V1-V2. Additionally, newly proposed criteria (loosening of the abnormal Q-wave duration criterion from ≥30 ms to ≥20 ms) for inferior infarcts may increase the prognostic value in these patients. (143)

Conclusions

The AW acuteness score is an ECG method for quantifying the acuteness of an evolving AMI. The score identifies patients in whom salvage can still be achieved independent of time from symptom onset, and thereby it may impact the triage decision of whether a patient should be rushed to pPCI or treated locally. Patients presenting late according to the ECG, and thus with no potential for salvage, may not need to be treated with the same urgency and acute transfer for pPCI. It would be interesting, but ethically very difficult, to do a future study randomizing patients presenting late by ECG to conservative treatment versus acute reperfusion. If this study showed that late presenters had similar survival benefit from conservative treatment versus acute reperfusion this approach would especially be of value in areas where pPCI is not ready available or only have limited capacity.
Additionally, the AW acuteness score can identify patients who currently are not offered pPCI due to late presentation, but who have potential for myocardial salvage if offered acute perfusion therapy. Busk et al.144 showed that 41% of STEMI patients presenting between 12-72 hours still had substandial myocardial salvage of >50% of the area at risk for infarction. It would be interesting to determine whether this group of patients also is early by ECG.
The implementation of the AW acuteness score in a larger scale or even routine clinical practice requires a large prospective trial using myocardial salvage estimated by MRI or SPECT, but probably even harder endpoints.

ST-SEGMENT ELEVATION

The presence of ST-segment elevation is the foundation for initiating reperfusion therapy in patients presenting with symptoms

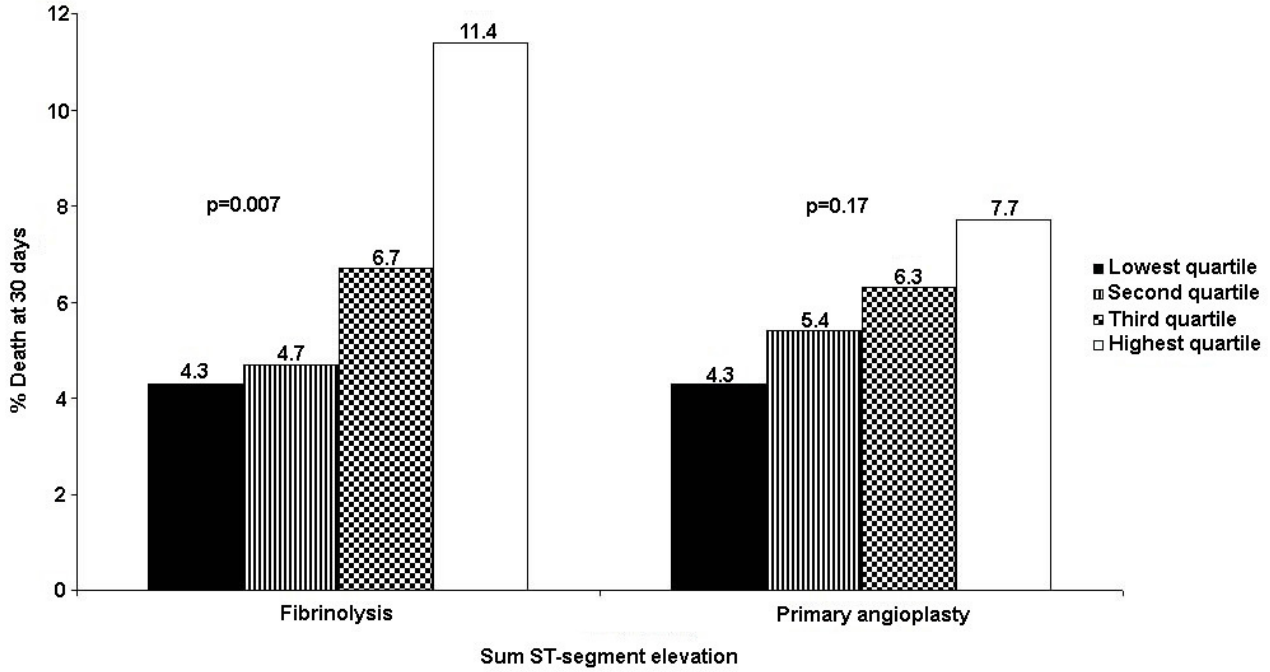

Figure 8
Mortality rates at 30-days for patients randomized to primary percutaneous coronary intervention or fibrinolysis. Patients are divided into quartiles of ST-segment elevation at baseline: First quartile: ≤6.5 mm; Second quartile: 7.0-9.5 mm; Third quartile: 10.0-14.5 mm; Fourth quartile: ≥15.0 mm
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suggesting ACS. Furthermore, several studies have demonstrated that the degree of ST-segment elevation on the admission ECG implies the extent of myocardium at risk of infarction, final infarct size, and prognosis. (14;145-148) Thus, the degree of ST-segment elevation remains pivotal for early risk stratification and initiation of treatment, including the preferred reperfusion strategy.

ST-segment elevation and outcome

Study V is a DANAMI-2 substudy aiming at determining the prognostic value of sum ST-segment elevation on the admission ECG, and secondly whether the prognostic value of ST-segment elevation differed between patients randomized to fibrinolysis versus pPCI. Patients were assigned to quartiles according to the sum of ST-segment elevation. The composite endpoint of death, reinfarction and stroke occurred more often in patients with the highest sum of ST-segment elevation. This was driven by a significant increase in mortality with increasing sum of ST-segment elevation, while neither reinfarction nor stroke rates were significantly related to the sum of ST-segment elevation. Accordingly, Willems et al. (148) found that patients with most ST-segment elevation (≥ 20 mm) had significantly larger infarcts and higher hospital mortality rates compared with those with less ST-segment elevation. Similarly, the Global utilization of strategies of open occluded coronary arteries (GUSTO) I trial found that the sum of absolute ST-segment deviation was one of the strongest predictors of mortality. (147) However, in another DANAMI-2 substudy we found that the manitude of ST-segment elevation was no longer an independent predictor of mortality when ECG "Grades of ischemia" (GI) was included in the logistic regression analysis. (149) GI consists of three grades: 1) Grade 1: tall upright T-waves; 2) Grade 2: ST-segment elevation in ≥2 adjacent leads without terminal QRS distortion, and 3) Grade 3: ST-segment elevation in ≥2 adjacent leads with terminal QRS distortion. This suggest that characterization of the quantitative changes occurring in the ST-segment and terminal portion of the QRS complex during the early stages of STEMI represents another and potentially better method for risk stratification in STEMI patients soon after presentation. (150)

In consensus with the results from the main DANAMI-2 trial all patients regardless of the quantity of ST-segment elevation upon presentation in Study V had fewer composite endpoints with pPCI than with fibrinolysis at 30 days, however the difference reached only statistical significance for patients in the highest ST-segment elevation quartile (≥15 mm). Additionally, only patients in the highest ST-segment elevation quartile showed a tendency towards better survival with pPCI, while the remaining patients had similar mortality rates regardless of treatment therapy (Figure 8). This finding is supported by earlier studies showing that the mortality benefit with pPCI versus fibrinolysis only are present among patients with a high risk profile. (151;152) Interestingly, we found in another DANAMI-2 substudy that patients violating the inclusion criterion of at least 4 mm of ST-segment elevation (≥2 mm in at least 2 of the leads I, aVL, V1-V6 or ≥1 mm in all 4 leads II, III, V5-V6, or ≥2 mm in at least 2 of leads II, III, V5-V6) showed a trend towards an increased 30-day mortality rate with pPCI suggesting an early hazzard with pPCI in patients with small infarcts. (153)

After fibrinolysis a residual stenotic lesion remains in 70-80% of patients (154;155) and 5-32% will reocclude. (156;157) In contrast, the presence of a residual stenotic lesion and the incidence of reocclussion after successful PCI are minimized with the routine use of stens and adjunctive pharmacological therapy. (158-160) In concordance with these findings it is not surprising that

patients treated with fibrinolysis had significant more reinfarctions than patients treated with pPCI regardless of ST-segment elevation. More reinfarctions were seen in patients with increasing ST-segment elevation in both treatment groups. This may partly be explained by anterior infarct location producing more ST-segment elevation compared to non-anterior infarcts, and that patients with anterior infarction have a higher reinfarction rate at late follow-up. (142;161) Additionally, Busk et al. (142) found that reinfarction was associated with small reference diameter of the target vessel and small minimal luminal diameter, which are both characteristics of the left anterior descending artery.
Risk factors for stroke include general atherosclerosis, cardiac disease, increasing age, diabetes, atrial fibrillation (AF), smoking, high blood pressure, and high body mass index (BMI). (162;163) Stroke has not been related to ST-segment elevation. Surprisingly, Study V showed that stroke occurred more frequently in fibrinolized patients in the lowest two ST-segment elevation quartiles. Although numbers were small, and significance was not attained, this observation is of concern and should be addressed in future studies investigating the occurrence of stroke. Cardiac disease is a known risk factor for stroke and significantly more patients in the first two ST-segment elevation quartiles had a prior MI compared to patients in the last two quartiles. There was no difference between quartiles in other risk factors for stroke.
The inherent limitation of Study V is the post-hoc design and few endpoints in several analyses increasing the risk of statistical type I and II errors. This makes the results hypothesis generating rather than conclusive. Another limitation is the exclusion of 122 patients due to missing baseline ECG or missing ST-segment measurements. Excluded patients had a worse risk profile with higher killip class ≥II (16% versus 8.4%, p=0.01) and more adverse events (20.5% versus 10.1%, p<0.001). Consequently, it is unknown whether the present findings can be applied to patients with a high risk profile.

Conclusions

Several studies have indicated that the magnitude of ST-segment elevation in the presenting ECG is an important predictor of final infarct size and outcome in patients with STEMI. The baseline ECG should therefore be integrated in the early decision making for patients presenting with STEMI. Our results indicate that all patients regardless of initial ST-segment elevation had better outcome with pPCI than with fibrinolysis. However, only patients with ST-segment elevation of ≥15 mm at presentation had a mortality benefit from pPCI, while the remaining patients achieved similar mortality rates regardless of treatment therapy. Urgent transfer for pPCI may then be unnecessary in patients with minor ST-segment elevation. This would especially be of value in areas with long transfer times to pPCI. However, since all fibrinolyzed patients have a significantly increased risk of reinfarction, systematic angiography and PCI after fibrinolysis are necessary regardless of the amount of ST-segment elevation at presentation. This approach is also adopted by the most recent guidelines.

CHAPTER 6

THE ECG FOR MONITORING AND OPTIMAL PREHOSPITAL CARE

Once the diagnosis of STEMI is established on a prehospital ECG, ECG monitoring and/or serial 12-lead ECG recordings are necessary for further observation of the patient. Any ECG changes will play an important role in the decision support for minimizing morbidity and mortality during transport to the receiving hospital. Accordingly, all Danish ambulances are capable of establishing continuous 12-lead ECG monitoring in addition to measuring saturation and blood pressure.

Early complications and safe ambulance transport in STEMI

Patients experiencing STEMI are in danger of dying within the first hours of symptom onset, typically by malignant ventricular arrhythmia or cardiogenic shock. Ventricular fibrillation (VF) is seen in 10% of STEMI patients (164), often within the first 4 hours of ischemia/infarction (165), while ventricular tachycardia (VT) is seen later on, often after 4 hours. (166) Consequently, the appearance of serious arrhythmic complications during ambulance transport is expected in STEMI patients in the early hours after symptom onset.
Inter-hospital transport of STEMI patients from a community hospital to a tertiary hospital for pPCI has been shown to be safe and feasible in several randomized trials. (42;47;167;168) In DANAMI-2 all transports were performed with a physician on board. (42) However, the physician tended to be junior staff to allow the most experienced physician to stay at the hospital. The physician was able to perform resuscitation and administer relevant medication according to the patient's condition, but usually not able to perform intubation. In DANAMI-2 with a transfer distance of 3-150 km (median 32 minutes) the overall complication rate was 6.4% (AF 2.5%; AV block 2.3%; VF 1.6%; deaths 0%). A similar rate of VF and deaths was found in the Primary angioplasty in patients transferred from general community hospitals to specialized PTCA units with or without emergency thrombolysis 2 (PRAGUE-2) trial. (47) However, higher complication rates are expected during ambulance transport in daily clinical practice because clinical randomized trials often fail to include the most unstable high risk patients.
Study III included consecutive patients diagnosed with STEMI in the ambulance and transferred directly for pPCI. One out of three was transported by an EMT ambulance while the remaining was accompanied by a physician-manned ambulance. The EMT ambulance had to request help from the physician-manned ambulance in cases of persistent arrhythmia, need for intubation, or cardiogenic shock. The summed arrhythmic complication rate of 10% (VF 4%; VT 2%; AV nodal re-entry tachycardia 1.2%; AV block 2/3 1.2%; pulseless electrical activity (PEA) 0.6%; AF 0.6%; bradycardia 0.6%), and a mortality rate of 1% were higher than in the DANAMI-2 trial. However, it is important to recognize that all cases were treated appropriately and a physician was present in both cases of ambulance deaths. Patients in Study III were only transported 1-22 km (median 11 minutes), and it is likely that the complication rate would increase with longer transport distances. Whether it is safe to transfer STEMI patients directly to a tertiary angioplasty center for pPCI without physician escort has not been fully investigated. A small Danish study employing risk stratification identified patients with a low risk of developing complications during direct transfer. (169) Eleven patients were judged unstable for direct transfer, while 71 patients were transferred (median 46 minutes) without a physician escort, and only one of these patients experienced VF (1.4%). The complication rate in Study III supports the presumption that the complication rate would have been considerable higher if risk stratification had not been employed and all patients had been transferred directly.
The Danish Society of Cardiology (170) recommends rendez-vous by a physician-manned ambulance in all transports of unstable STEMI patients (persistent arrhythmia, need for intubation, or cardiogenic shock) and rendez-vous if possible when transporting stable STEMI patients.

Conclusions

Complications are expected in the early hours after the manifestation of STEMI, and consequently safe ambulance transport is pivotal. Our results show a high frequency of arrhythmias in STEMI patients during even short transport distances. However, these complications can be treated with a setup combining EMT ambulances with physician-manned ambulances in urban areas. Ambulances manned by EMT are the most common type of ambulances in Denmark. Consequently, the vast majority of patients diagnosed with STEMI will be treated by an EMT-basic ambulance, which can defibrillate when needed but only administer oral aspirin, oral nitro-glycerin, and oxygen. A new level of education for ambulance personnel (paramedics) is emerging in Denmark. (83) Paramedics are educated in administrating intravenous medication and will, in addition to defibrillation, therefore be able to treat the most common arrhythmic complications by intravenous medication.

In areas with longer treatment times application of risk stratification to determine whether patients can be transported for pPCI with or without physician escort may be appropriate. However, the time delay emerging when patients are taken to a local hospital to acquire a physician escort, must be evaluated against the advantage of transporting the patients directly to the catheterization laboratory for initiation of the earliest treatment possible, including mechanical reperfusion, and left ventricular assist devices when needed. Currently, a study evaluating the complication frequency during ambulance transport and the need for assistance by a physician-manned ambulance in the Region of Zealand with transport times up to 3 hours is being planned. With this study we hope to gain focus on the importance of safe ambulance transfer.

ANTITHROMBOTIC THERAPY FOR OPTIMAL PREHOSPITAL CARE

Time to reperfusion in STEMI patients can be significantly reduced when a prehospital ECG, as the basis for decision support, is transmitted to a cardiologist for early diagnosis and triage. Once the STEMI diagnosis is established and the patient is triaged for pPCI, intensive anticoagulant and antiplatelet drug therapy must be initiated acutely to secure best possible outcome for the patient. The goal is to inhibit the thrombotic process, and reduce the risk of later reocclusion. The key is to identify the combination of antithrombotic drugs, that are the most effective at reducing thrombosis, but also provide a good safety profile.

Bleeding as a consequence of treatment

Major bleeding is currently the most common non-cardiac complication of therapy in patients with ACS. In general physicians tend to rate ischemic complications more severely than bleeding complications, since the later can be limited by discontinuation of treatment. However, bleeding complications as well as the need for transfusion are strongly associated with both morbidity and mortality. (171-174) Consequently, there is a need to decrease the rate of bleeding complications. The relationship between bleeding and increased morbidity and mortality is not clear but may result from an increase in ischemic events due to the activation of clotting, the pausing of antithrombotic therapies due to bleeding, or the adverse effects seen with hypotension, and transfusion.

The risk of bleeding is not the same for thrombolytic-, anticoagulant-, and antiplatelet drugs, and is influenced by how they may be combined, but also by the clinical situation. The antithrombotic efficacy of a drug is often assumed to be directly linked to its risk of bleeding, however clinical data do not support this. Accordingly, aspirin and streptokinase led to similar reductions in mortality rates in ISIS-2, but only streptokinase led to an increased risk of intracranial hemorrhage or the need for transfusion. (35)

Current prehospital pharmacological therapy

In Denmark the current prehospital treatment of STEMI patients transferred for pPCI, includes aspirin, clopidogrel, and heparin followed by GPI during the invasive procedure. These drugs have reduced the rate of thrombotic complications in randomized clinical trials, but due to their mode of action they all increase the patient's risk of bleeding.

Aspirin is an anti-platelet agent targeting the cyclo-oxygenase-1 receptor and thereby blocking the formation of thromboxane A2 in the platelet cascade. Thromboxane A2 is a powerful promoter of platelet aggregation, and by blocking it, platelet aggregation is prevented. Aspirin is a cornerstone in the therapy of STEMI patients because it reduces the rate of vascular events including nonfatal MI, nonfatal stroke, and death. (175) By reducing mortality, thrombotic complications during PCI, and the risk of later stent thrombosis, administration already in the prehospital setting is recommended. (48;49) However, since aspirin only targets one receptor it should be combined with other therapies like the ADP receptor blocker clopidogrel.

Clopidogrel is a pro-drug metabolized in the liver by the cytochrome P450 isoenzyme A4. The active metabolite targets the P2Y12 receptor and thereby ADP-induced platelet aggregation.176 The full antiplatelet effect of clopidogrel is achieved within 2 hours after a 600 mg loading dose. (177) Studies (178;179) have shown that pretreatment with clopidogrel in pPCI improves outcome justifying aplication already in the prehospital setting. However, administration in the prehospital setting is only common in Europe and not in the USA where administration is often postponed until after catheterization, and the need for CABG is ruled out. (180)

Unfractionated heparin is an indirect thrombin inhibitor requiring the presence of antithrombin III. Unfractionated heparin only inhibits soluble, and not clot-bound thrombin, and at the same time activates platelets causing the need for antiplatelet strategies. However, heparin has remained the primary antithrombotic therapy for prevention of periprocedual ischemic complications during PCI. (181) Together with aspirin prehospital administration of heparin results in better TIMI flow in the IRA, and thereby a higher angioplasty success rate, a smaller enzymatic infarct size, higher ejection fraction (EF), and lover 30-day mortality. (182) Since the DANAMI-2 trial the heparin dose given in Denmark has been arbitrary set at 10.000 IU for STEMI patients undergoing pPCI.42 However, according to guidelines a weight-adjusted dose of 70 IU/kg, or 50-60 IU/kg when GPI is given, is more appropriate. (181)

In addition to heparin a GPI is recommend as standard treatment during pPCI. (181) The most effective timing of GPI administration has been investigated with conflicting results. The Facilitated intervention with enhanced reperfusion speed to stop events (FINESSE) trial (183) showed no benefit of prehospital abciximab, while a meta analysis by De Luca et al. (184) demonstrated improved survival with early versus late administration. Recently, the Ongoing tirofiban in myocardial infarction evaluation 2 (On-

Table 5 Definition of bleeding according to the Acute Catherterization and Urgent Intervention Triage Strategy (ACUITY) criteria[190]

ACUITY criteria	
Significant bleeding	Intracranial
	Retroperitoneal
	Intraocular
	Access site haemorrhage requiring radiological or surgical intervention
	≥5 cm diameter haematoma at puncture site
	Reduction in haemoglobin concentration of of ≥2.5 mmol/L without an overt source of bleeding
	Reduction in haemoglobin concentration of ≥1.9 mmol/L with an overt source of bleeding
	Surgery due to bleeding
	Use of any blood product transfusion
Minor bleeding	All other bleeding

TIME 2) trial (185) showed that a high-dose bolus regimen of the GPI tirofiban administred prehospitally improved ST-segment resolution compared to placebo. However, there was no significant difference in bleeding and clinical outcome after pPCI. The largest effect was seen when patients received tirofiban shortly after onset of symptoms. In a DANAMI-2 substudy we showed that the GPI abciximab, administred during pPCI or as bailout was an independent predictor of partial ST-segment resolution as a measure of better microvascular perfusion. (186)
The GPI blocks the platelets' glycoprotein receptor and thereby effectively inhibits the last part of the platelet aggregation process. (187) It reduces 30-day mortality and reinfarction, as well as 6-month mortality and major adverse cardiac events (MACE). (159;188) However, the beneficial effect is compromised by an increased risk of major bleeding complications. (159)

Prehospital bivalirudin

Prehospital bivalirudin may be an alternative to heparin plus GPI. It has been shown to be comparable to heparin plus GPI regarding rates of ischemic events, but significantly reduces the risk of bleeding complications in patients with ACS. (189-191) Accordingly, the most recent guidelines recommend that STEMI patients undergoing PCI, who are at high risk of bleeding, are treated with bivalirudin. (50)
Bivalirudin binds specifically but reversible to thrombin and thereby inhibits both free and clot-bound thrombin preventing both the initiation and the continuation of clot formation, which is most favorable in STEMI patients, who already have a thrombus burden. Additionally, thrombin mediated platelet activation and aggregation are prevented. (192) Another advantage is no interaction with heparin antibodies (193), and a short half-life of 25 minutes with linear dose-and-concentration dependant anticoagulation activity. (192)
If heparin in combination with GPI is to be replaced with bivalirudin then administration already in the prehospital phase immediately after the STEMI diagnosis is established would be ideal. With its ease of administration and storage that does not require refrigeration bivalirudin has ideal characteristics for prehospital use. Also in the minority of patients referred for acute CABG the short half life is advantages. The use of bivalirudin has been shown to lower in-hospital costs by >$400 when compared to heparin and GPI. (194) Consequently, large savings for the entire healthcare system can be achieved if the use of prehospital bivalirudin reduces bailout with GPI.
To our knowledge Study VI is the first study to bring bivalirudin into the ambulance determining its feasibility and safety in the prehospital setting. We included 102 patients treated with bivalirudin and 72 treated with heparin. All patients were diagnosed with STEMI and triaged for pPCI by prehospital ECG transmission to a cardiologist. Implementation of bivalirudin instead of heparin did not increase on scene time in Study VI even though new procedures often tend to be more time consuming.
The small study population did not allow us to detect any differences in clinical outcome in patients treated with bivalirudin versus heparin plus GPI. However, TIMI 3 flow before the procedure was seen in almost twice as many patients treated with bivalirudin (20% versus 12%), and almost twice as many patients in the heparin group had major bleeding (10% versus 6%). The frequency of major bleeding in Study VI corresponds well to the results of the Harmonizing outcomes with revascularization and stents in acute myocardial infarction (HORIZONS-AMI) trial (n=3602), where major bleedings increased from 4.9% in the bivalirudin group to 8.3% in the heparin plus GPI group. (191) This was the first trial to investigate bivalirudin in STEMI patients during pPCI. Usually bleeding complications in randomized clinical trials evaluating antithrombotic therapies are classified according to different bleeding criteria making it difficult to compared treatment strategies, but the Acute catherterization and urgent intervention triage strategy (ACUITY) criteria (190) were used in both HORIZONS-AMI and Study VI (Table 5).
A limitation of Study VI is the non-randomized nature and the use of a historic control group. Preferable patients should have been randomized to either prehospital heparin or bivalirudin once the STEMI diagnosis had been established by prehospital ECG transmission. However, the approach of informed patient consent would have increased prehospital times considerable in Study VI where transport times to the tertiary hospital were median 9 minutes. A historic control group can confound the results, since

changes in treatment therapy may have occurred over time. Ninety percent received a stent in the heparin group versus 76% in the bivalirudin group. This difference may be related to improved thrombin inhibition with bivalirudin, resulting in less thrombus burden in the culprit artery, and thereby less inclination of the PCI operator to use a stent. This assumption is supported by the trend of more patients with TIMI 3 flow before the procedure in the bivalirudin group. In contrary, the difference may also be explained by a change in the PCI operators' preference for the use of drug eluting stents after the World Congress of Cardiology 2006 where drug eluting stents were suggested to increased the risk of late stent-thrombosis. However, a resent search in the "invasive procedure database" (Patient analysis and tracking system, Dendrite Systems (PATS), Playhatch, United Kingdom) used at the Department of Cardiology, Rigshospitalet showed that the overall frequency of stent placement in 2006 and 2007 was 90% and 88%, respectively, and thus not reduced after the World Congress of Cardiology 2006 (Personal communication).
In addition to prehospital drug therapy remote ischemic preconditioning performed in the ambulance by inflation of a blood pressure cuff causing upper limb ischemia may also optimize patient care as it has been shown to increase myocardial salvage and reduce final infarct size. (195) The method is thought to reduce the injury seen with reperfusion and thereby harness the full benefit of reperfusion therapy.

Conclusions

Prehospital ECG recording followed by transmission to a cardiologist is the key not only for a correct STEMI diagnosis and appropriate triage, but also for the initiation of appropriate prehospital therapy. The most optimal pharmacological cocktail for improving outcome in STEMI patients treated with pPCI is yet to be found, and new therapies are introduced hoping that they will improve prognosis without side effects. Study VI showed that prehospital administration of bivalirudin may be an attractive alternative to treatment with heparin plus GPI. However, the superiority of bivalirudin needs confirmation in
the ongoing large multicenter randomized European ambulance acute coronary syndrome angiox trial (EUROMAX) comparing outcome in 3680 patients randomized to prehospital bivalirudin versus heparin ± routine or bailout GPI.

CHAPTER 7

THE ECG AS DECISION SUPPORT FOR FURTHER THERAPY

After reperfusion therapy the key is to identify patients in whom therapy has been ineffective so further therapy can be initiated. One way is to determine the presence of myocardial tissue perfusion, which has been evaluated by several modalities e.g.: myocardial contrast echocardio-graphy (196), MRI (197), position emission tomography (PET) (198), SPECT (199), and ST-segment resolution. (200;201) However, the latter is the only method readily available to the clinician at bedside. ECG recorded before and after reperfusion may therefore provide the clinician with vital prognostic information which can help defining a target population in need for further therapeutic interventions.

ST-segment resolution analysis

ST-segment resolution starts occurring immediately after reestablishment of nutrient coronary blood flow to the ischemic area. ST-segment resolution is not only considered a marker of epicardial blood flow but also microvascular perfusion, and persistent ST-segment elevation, despite TIMI flow grade 3 in the coronary artery, is associated with an increased risk of death. (200;201) Complete ST-segment resolution after reperfusion therapy is then a result of successful reperfusion at both the epicardial and microvascular level. Conversely, persistent ST-segment elevation appears to be indicative of either an occluded IRA or a patent IRA with failure of myocardial perfusion.
The 2007 STEMI focused update uses the binary cut point of 50% ST-segment resolution as a marker for successful reperfusion. (49) However, division into 3 groups is also an establish method for estimating reperfusion success. (202;203) The 3 groups are classified as: 1) Complete resolution: >70% ST-segment elevation resolution, 2) Partial resolution: ≥30 to ≤70% ST-segment elevation resolution, and 3) No resolution: <30% ST-segment elevation resolution.
Yet different approaches have been used for ST-segment resolution analysis including sum of all or some leads with ST-segment elevation, sum of both ST-segment elevation and reciprocal ST-segment depression, and the single lead with the greatest baseline ST-segment deviation. (204;205) Interestingly, the simple method of residual ST-segment elevation in the most affected lead on the post-pPCI ECG performs at least as well as more complex methods requiring comparison of pre- and post-pPCI ECG or calculation of summed ST-segment deviation in multiple leads. (204-207)
In Study VII we chose to determine sum of all leads with ST-segment elevation, and used the 30% and 70% cut-off points for the ST-segment resolution analysis, because this strategy has been shown to be a strong predictor of outcome. (202;203;208) ST-segment elevation will normalize in all patients within 12 hours of symptom onset. (209) However, to facilitate a rapid decision regarding further therapy guidelines recommend reassessment of ST-segments 60-90 minutes after initiation of fibrinolysis. (49;181)
ST-segment resolution after fibrinolysis versus pPCI
The frequency of TIMI 3 flow is higher with pPCI compared to fibrinolysis (210;211), but the relationship between the mode of reperfusion and ST-segment resolution is still unclear. The first purpose of Study VII was to determine whether early ST-segment resolution differed in patients treated with pPCI versus fibrinolysis. We found that ST-segment resolution was more pronounced with pPCI versus fibrinolysis both prior to and 90 minutes after initiation of reperfusion therapy, while the difference had disappeared at 4 hours.
The difference in ST-segment resolution before treatment in the two treatment groups may be explained by a difference in the timing of aspirin and heparin. Primary PCI patients received aspirin and heparin at the local hospital before referral, while fibrinolyzed patients received aspirin and heparin immediately preceding fibrinolytic treatment. Consequently, 12% versus 6% (p=0.004) had ST-segment resolution prior to initiation of reperfusion therapy. In a previous study 25% of patients treated with aspirin and heparin prior to pPCI had complete ST-segment resolution. (212) The difference in ST-segment resolution at 90 minutes is probably related to the difference in time from initiation of therapy to artery patency with the two reperfusion strategies (see below).

ST-segment resolution and outcome

The second purpose of Study VII was to determine whether the prognostic value of ST-segment resolution differed with the mode of revascularization therapy being mechanical or pharmacological

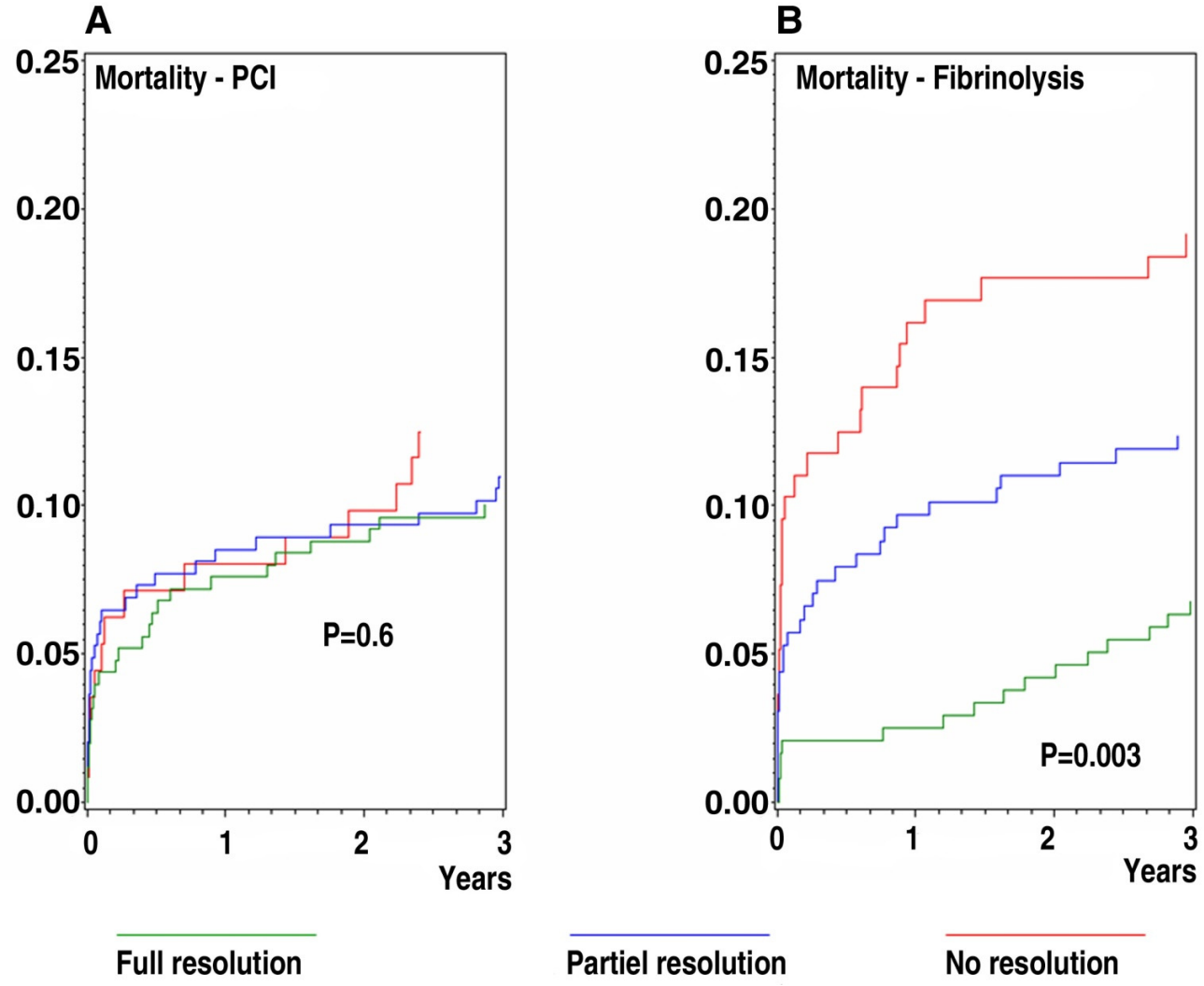

Figure 9
Kaplan-Meier curves illustrating mortality rates in primary percutaneous coronary intervention (pPCI) and fibrinolysis. The green line indicates full ST-segment resolution, the blue line indicates partial ST-segment resolution, and the red line indicates no ST-segment resolution.
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in a large STEMI population. Regardless of treatment strategy all patients with complete ST-segment resolution tended to have the lowest mortality rate, but this difference only reached statistical significance in patients treated with fibrinolysis. Accordingly, ST-segment resolution after thrombolysis has been proved to be a potent predictor of mortality, left ventricular function, final infarct size, and congestive heart failure. (202;203;213)
In contrast to our findings several studies have reported a relationship between the relative reduction in summed ST-segment elevation and outcome following pPCI. (200;204;214-216) Accordingly, the recent Thrombus aspiration during percutaneous coronary intervention in acute myocardial infarction study (TAPAS) showed a significant relationship between ST-segment resolution 30-60 minutes after PCI and 30-day mortality or MACE. (214) The discrepancy between our study and previous studies may be explained by the timing of the post procedure ECG which were recorded at a later point in time (90 minutes and 4 hours) in our study.

ST-segment resolution is traditionally determined at 90-180 minutes after initiation of fibrinolysis (201;217;218), while the optimal timing proceeding pPCI is uncertain. Given the immediate coronary artery patency with pPCI, ST-segment resolution may need to be determined at a much earlier time point. Accordingly, ECG recorded immediately post-PCI have more resemblance to a 90-minute ECG in patients receiving fibrinolytics, because needle to reperfusion with fibrinolysis is approximately 45 minutes. Study VII was not designed to address this issue, but the difference in timing may have favored ST-segment resolution in the pPCI group at 90 minutes, and additionally explain why Study VII, with the earliest available post-procedure ECG recorded after 90 minutes, only detected a relationship between ST-segment resolution and outcome for fibrinolyzed patients.
Terkelsen et al. (212) have questioned the value of the conventional 90-minute ECG after PCI, and suggested that ST-segment resolution must be determined at 30-minutes post-PCI to possess prognostic value. This is supported by a study showing that ST-segment resolution only differed at 30 minutes, and not at 60 and

90 minutes, in patients with normalized vs. impaired myocardial tissue perfusion after PCI. (219) In contrast, ECG recorded up to 3-4 hours after pPCI have been shown to be of prognostic value when residual ST-segment measures are used. (205-207)
In conclusion, ECG timing and the method for determining ST-segment deviation are essential to obtain prognostic value when ST-segment measures are used as a surrogate endpoint in large randomized trials. It may be speculated whether the optimal time point for ST-segment measurements is individual. If this is the case continuous ST-segment monitoring would be optimal. This would also allow for early detection of recurrent ST-segment elevation caused by reocclusion as seen in acute stent thrombosis.

Complete ST-segment resolution
Interestingly, Study VII showed that fibrinolyzed patients with complete ST-segment resolution seemed to have a much lower mortality rate compared to patients receiving pPCI both with and without ST-segment resolution (Figure 9). However, this mortality benefit by fibrinolysis seemed to be counterbalanced by an increased risk of reinfarction in patients with complete ST-segment resolution. Similar findings have been reported by De Lemos et al. (220) This relationship of complete ST-segment resolution with a high reinfarction rate may be explained by a difference in aetiology for patients with and without complete ST-segment resolution. Patients with complete ST-segment resolution may be experiencing a large acute occlusion which when removed by fibrinolysis is leaving a vulnerable plaque prone to reinfarct later. In contrast, patients with no ST-segment resolution have no or only minor viable myocardium exposed for later reinfarction. Based on these finding all fibrinolyzed patients irrespective of the degree of ST-segment resolution seem to have a better prognosis with subsequent PCI. Accordingly, PCI in patients with failed fibrinolysis has been shown to improve outcome, including a reduction in reinfarction rate. (221;222) As mentioned earlier (see page 6) this approach is supported by recent guidelines recommending transfer of all fibrinolyzed high risk patients to a PCI-capable facility, and consideration of transfer even if patients are not at high risk, especially if symptoms persist and failure to reperfusion is suspected. (50) However, caution should be taken regarding both timing and what fibrinolytic regime to use since facilitated PCI has been shown to increase stroke rate, ischemic cardiac complications, heart failure, shock, and mortality rates. (223)

Conclusions
The ECG is pivotal for STEMI diagnosis. ST-segment elevation is diagnostic in these subjects, and larger summated ST-segment elevation is associated with a higher mortality rate. Many studies of reperfusion, in particular fibrinolysis, have shown a relationship between ST-segment resolution and improved outcomes. Our study was the hitherto largest comparison of ST-segment resolution as prognosticator in a randomized trial of thrombolysis versus pPCI. Complete ST-segment resolution was associated with the lowest mortality rate in all patients, but this difference only reached statistical significance in patients treated with fibrinolysis. By demonstrating this relationship in fibrinolyzed patients the ECG remains an important tool for risk stratification in this group of patients, and may help select patients in need for adjunctive PCI. The present results indicate that ECG recorded at 90-minutes and 4-hours do not provide help in risk stratification of patients treated with pPCI. Until this finding has been investigated further, relative ST-segment resolution in ECG recorded 90 minutes or later after PCI may not be a good surrogate endpoint for outcome in clinical trials.
Interestingly, we found that patients with compete ST-segment resolution treated with fibrinolysis had the highest risk of reinfarction which emphasizes the need for considering PCI in all patients even after successful fibrinolysis. Our results are limited by the post-hoc design. Additionally, not all STEMI patients were included in the DANAMI-2 trial making generalization of the results an issue. On the other hand the results are strengthened by the fact that the DANAMI-2 trial was a very large clinical trial with few drop-outs, long clinical follow-up, and few cross-overs.

CHAPTER 8
SUMMARY
The electrocardiogram (ECG) can be used for determining the presence, location and extent of jeopardized myocardium during acute coronary occlusion. Accordingly, the ECG has become essential in the treatment of patients with acute coronary syndrome (ACS). This thesis aims at optimizing the decision support, provided by the ECG, for choosing the best treatment strategy in the individual patient with ST-segment elevation acute myocardial infarction (STEMI).
ECG recorded in the prehospital setting has become the standard of care in many communities, but to achieve the full advantage of this early approach it is important that the ECG is recorded from accurately placed electrodes to produce an ECG that resembles the standard 12-lead ECG. Accurate electrode placement is difficult especially in the acute setting, and we investigated an alternative lead system with fewer electrodes in easily identified positions. We showed that the system produced waveforms similar to the standard 12-lead ECG. However, occasional diagnostic errors were seen, compromising general acceptance of the system.
Once the ECG has been recorded a decision regarding triage must be made on the basis of a correct ECG diagnosis. We found that trained paramedics can diagnose STEMI correctly in patients without ECG confounding factors, while the presence of ECG confounding factors decreased their ability substantially. Consequently, since many patients do present with ECG confounding factors, transmission to an on-call cardiologist for an early correct diagnosis is needed. We showed that time to pPCI was reduced by more than 1 hour by transmitting prehospital ECG to a cardiologist's handheld device for diagnosis, triage, and activation of the catheterization laboratory when needed.
The optimal treatment strategy is dependent on the duration of ischemia however patient information is often inaccurate. Accordingly, it would be advantageous if the first available ECG can help identify patients who will benefit greatly from acute reperfusion therapy versus patients with modest effect. We showed that by recognizing the acuteness of the infarction process the initial ECG can identify a group of patients with no potential for myocardial salvage despite short symptom duration. Urgent transport for pPCI may then not be necessary in this group of patients, and conservative treatment may be an option. Conversely, we also identified a group of patients with a large potential for myocardial salvage with acute reperfusion therapy despite long symptom duration.
We also investigated whether ST-segment elevation on the initial ECG could provide prognostic information and thereby decision support for appropriate triage. All patients regardless of ST-segment elevation seemed to have most clinical benefit from pPCI. However, only patients with the greatest amount of ST-

segment elevation had a reduced mortality rate with pPCI suggesting that patients with minor infarcts may achieve similar benefit from fibrinolysis followed by transfer to angiography and PCI.

Once the triage decision is settled, STEMI patients must undergo ECG monitoring and receive antithrombotic therapy for optimal prehospital care. STEMI patients transported over even short distances are in danger of developing arrhythmic complications, but appropriate treatment is available when primary ambulances are supported by physician-manned ambulances in urban areas. Prehospital antithrombotic therapy must be effective in preparing the patient for pPCI without causing bleeding. Heparin is currently the standard therapy, but we showed that the direct thrombin inhibitor bivalirudin may be an attractive alternative by causing less bleeding events, and a higher frequency of preprocedure thrombolysis in myocardial infarction (TIMI) 3 flow.

After reperfusion therapy a decision regarding the need for further treatment is desirable. By determining ST-segment resolution in the post-reperfusion ECG we showed that the degree of ST-segment resolution at 90 minutes and 4 hours is important for risk stratification after fibrinolysis, but not after pPCI. Interestingly, we found that patients with compete ST-segment resolution treated with fibrinolysis had the highest risk of reinfarction. Consequently, transfer to a PCI-facility should be considered in all patients treated with fibrinolysis as the initial reperfusion therapy.

Based on the findings in the present thesis we conclude that the ECG is an important tool for decision support in every step from symptom onset to post-reperfusion therapy in STEMI patients.

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