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ACUTE MYOCARDIAL INFARCTION – EARLY DIAGNOSIS AND THE PROGNOSTIC VALUE OF ECG AND ECHOCARDIOGRAPHY

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Acute Myocardial Infarction – Early Diagnosis and the Prognostic Value of ECG and Echocardiography
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“Please be on time! Early = on time, on time = late, late = really late.”
Internationella Engelska Skolan

ABSTRACT

Introduction

Acute myocardial infarction (AMI) is a main cause of death. Despite vast improvements in management and treatment strategies over the past decades, morbidity and mortality after an AMI remains high. For patients with AMI and ST-segment elevations (STEMI), urgent management has been shown to be associated with reductions in both morbidity and mortality. Various pre-hospital management strategies have been implemented, during which STEMI patients can be referred directly to the catheterization laboratory instead of first being assessed in the emergency department. Valuable minutes can thus be saved. However, it is important that the diagnosis is correct which can be more challenging in a setting where the referring cardiologist is not at the same location as the patient and the clinical setting therefore needs to be reported by the paramedic staff. Studies on the accuracy of pre-hospital STEMI diagnoses are limited. In order to expedite management for STEMI patients, international guidelines have included benchmark time targets. Little is known regarding gender differences in the achievement of these time targets, and the feasibility of obtaining a pre-hospital ECG within ten minutes of ambulance arrival has been questioned.

For patients who survive an AMI, there is a risk of transient or permanent damage to the left ventricle. Such damage can be quantified by echocardiography. It is shown that patients with a reduced left ventricular ejection fraction (LVEF) have a higher risk of sudden cardiac death than patients with normal LVEF. For patients with reduced LVEF despite optimal medical treatment, an implantable cardioverter defibrillator (ICD) can reduce mortality. This benefit is not seen until after several months have passed since the AMI. This is further complicated by the fact that the risk of death is highest in the early days, weeks and months after an AMI. Therefore, finding predictors in the early phase after an AMI, preferably while the patient is still admitted to the ward, would likely be beneficial in the selection of patients for ICD treatment.

Aims

The overall aim of this thesis was to find easily obtainable measurements by ECG and echocardiography that could improve the prognosis for patients with acute myocardial infarction. More specifically, the aim was to study the rate of false-positive STEMI diagnoses based on pre-hospital ECGs (study I), study gender differences in time intervals and adherence to guideline set time targets (study II), study the predictive value of low-dose dobutamine stress echocardiography on the improvement of LVEF (study III) and investigate the use of discharge ECG in the early prediction of ICD candidates (study IV).

Methods

In study I all patients for whom a pre-hospital ECG had been transmitted to the investigating hospital during 2013 were included. In study II, patients with a STEMI diagnosis and a pre-hospital ECG between December 2010 and July 2015 were included. Information on whether a pre-hospital STEMI diagnosis had been set or not was collected from medical charts and the final diagnosis of STEMI was found in the national quality registry SWEDEHEART. For both study I and study II, information on time intervals were collected from ambulance charts, medical charts, a database collecting information on pre-hospital ECGs, and SWEDEHEART.

In studies III and IV, adult patients with an at least moderately reduced left ventricular function (defined as LVEF $\leq 40\%$) with a life expectancy of more than one year and who were admitted for AMI were invited and followed by clinical visits and echocardiographic examinations. In study III, a low-dose dobutamine stress echocardiogram was performed within one week of the AMI and in study IV, the discharge ECG was reviewed.

Results

In study I, 16% (95% CI 10 – 23) out of 115 patients with a suspected STEMI based on pre-hospital ECGs were discharged with alternative diagnoses. Measured as the time from ambulance arrival at the patient's location, the time target of reperfusion therapy within 90 minutes was achieved for almost all patients (98%), but the achievement of a pre-hospital ECG within ten minutes was only met for 16% of the cohort. The delay time to pre-hospital ECG was significantly longer for women than for men, 20 vs. 13 minutes ($p < 0.001$).

In study II, 539 patients with STEMI and a pre-hospital ECG were included. A pre-hospital ECG was obtained within ten minutes for 22% of the cohort, and the target was more likely to be achieved for men than for women (29% vs. 14%, $p = 0.001$). Among all patients, 88% reached the target of reperfusion therapy within 90 minutes and there was no difference between men and women. Women had a significantly longer delay time between symptom onset and emergency call than men (median 61 vs. 45 minutes, $p = 0.031$).

In study III, among 96 patients with an at least moderately reduced LVEF after an AMI, 60% had an LVEF $\geq 35\%$ after three months. Patients with an LVEF $\leq 35\%$ after three months had a significantly lower left ventricular function at both resting and stress echocardiography, measured as LVEF, mitral annular plane systolic excursion (MAPSE) and peak systolic velocity (PSV). Baseline LVEF was a good predictor of recovery with a C-statistic of 85% (95% CI 74 – 94). None of the other variables, including the stress echocardiography variables, were better discriminators.

In study IV, 87 patients with LVEF $\leq 40\%$ after an AMI were included. Patients who had a pathologic R-wave progression on the discharge ECG were four times more likely to receive

an ICD than those with normal R-wave progression (HR 4.0, 95% CI 1.1-14.3, p = 0.033). None of the patients without a pathologic R-wave progression, pathologic Q-waves, or intra-ventricular conduction abnormalities, received an ICD or suffered from malignant arrhythmias during the follow-up period.

Conclusions

The rate of false-positive catheterization laboratory activations based on pre-hospital STEMI diagnoses is well in comparison to rates reported based on in-hospital triage. Still, there are gender differences favoring men in regards of delay time from symptom onset to emergency call and ambulance arrival to pre-hospital ECG. The target of obtaining a pre-hospital ECG within ten minutes is met for only around one fifth of the patients, and improvements regarding this are warranted. For patients with heart failure after an AMI, baseline LVEF is a strong predictor of improved recovery while simple measurements of LVEF, MAPSE and PSV during low-dose dobutamine stress echocardiography did not add prognostic information. Patients with a pathologic R-wave progression have a significantly higher risk of receiving an ICD, and patients without pathologic R-wave progression, or Q-waves, or intra-ventricular conduction abnormalities are unlikely to receive an ICD and could be seen as a low-risk population.

LIST OF SCIENTIFIC PAPERS

I. Muhrbeck J, Persson J, Hofman-Bang C. Catheterization laboratory activations and time intervals for patients with pre-hospital ECGs. Scandinavian Cardiovascular Journal. 2018 Apr;52(2):74-79.

II. Muhrbeck J, Maliniak E, Eurenius L, Hofman-Bang C, Persson J. Few with ST-segment elevation myocardial infarction are diagnosed within 10 minutes from first medical contact, and women have longer delay times than men. International Journal of Cardiology Heart & Vasculature. 2020 Jan 2;26:100458.

III. Muhrbeck J, Günyeli E, Andersson E, Alam M, Frykman V, Sjöblom J. Does stress echocardiography add incremental value to baseline ejection fraction for the early identification of candidates for implantable defibrillators? Open Heart. 2019 Jul 11;6(2):e001053

IV. Muhrbeck J, Frykman V, Alam M, Sjöblom J. Early ECG signs after an acute myocardial infarction to identify candidates for Implantable Cardioverter-Defibrillators. *Manuscript*.

CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS

AMI	Acute Myocardial Infarction
ARIC	The Atherosclerosis Risk in Communities
AUC	Area Under the Curve
AVID	Antiarrhythmic Versus Implantable Defibrillator
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CASH	Cardiac Arrest Study Hamburg
CCU	Coronary Care Unit
CHA_2DS_2 VASc	Congestive Heart Failure, Hypertension, Age ≥ 75, Diabetes, Stroke or Tia, Vascular Disease, Age 65-74, Sex category
CHS	The Cardiovascular Health Study
CI	Confidence Interval
CIDS	Canadian Implantable Defibrillator Study
CIE	Computer-Interpreted Electrocardiogram
CL	Catheterization Laboratory
COMPANION	Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure
CRT-D	Cardiac Resynchronization Therapy – Defibrillator
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Pectoris Suppress Adverse Outcomes with Early Implementation of The American College of Cardiology / American Heart Association Guidelines
cTn	Cardiac Troponin
CVD	Cardiovascular Disease
DINAMIT	Defibrillator In Acute Myocardial Infarction Trial
ECG	Electrocardiogram
ED	Emergency Department
e.g.	*Exempli gratia*

EMS	Emergency Medical Services
ESC	European Society of Cardiology
et al.	*Et alia*
FMC	First Medical Contact
FITT-STEMI	Feedback Intervention and Treatment Times in ST-elevation Myocardial Infarction
Gusto-IIb	Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes
HR	Hazard Ratio
ICD	Implantable Cardioverter Defibrillator
IHD	Ischemic Heart Disease
IRIS	Immediate Risk-Stratification Improves Survival
ISACS-TC	International Survey of Acute Coronary Syndromes in Translational Countries
LDL	Low-Density Lipoprotein
LBBB	Left Bundle Branch Block
LVEF	Left Ventricular Ejection Fraction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MAPSE	Mitral Annular Plane Systolic Excursion
MUSTT	Multicenter Unsustained Tachycardia Trial
NYHA	New York Heart Association
OR	Odds Ratio
PAR	Population Attributable Risk
PCI	Percutaneous Coronary Intervention
PSV	Peak Systolic Velocity
RBBB	Right Bundle Branch Block
ROC	Receiver Operating Characteristic
SCD	Sudden Cardiac Death
SCD-HeFT	Sudden Cardiac Death – Heart Failure Trial
SCAAR	The Swedish Coronary Angiography and Angioplasty Register

SCORE	Systemic Coronary Risk Evaluation
STEMI	ST-segment Elevation Myocardial Infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Treatment
TRAPID-AMI	High Sensitive Cardiac Troponin T Assay for Rapid Rule-Out of Acute Myocardial Infarction
VALIANT	Valsartan in Acute Myocardial Infarction Trial
VF	Ventricular Fibrillation
vs.	versus
VT	Ventricular Tachycardia
WHO	World Health Organization

1 INTRODUCTION

1.1 PREAMBLE

For patients with certain types of acute myocardial infarction (AMI), rapid and correct management and treatment can reduce the risk of death and heart failure. Despite efforts, the risk of ischemic heart failure after an AMI remains significant. If heart failure persists despite optimal medical treatment, an implantable cardioverter defibrillator (ICD) can reduce mortality. Earlier and more precise identification of patients suitable for ICD treatment is also likely to reduce mortality. In this thesis, these aspects will be discussed and explored further.

1.2 EPIDEMIOLOGICAL ASPECTS

Cardiovascular disease (CVD), and especially ischemic heart disease (IHD), is the leading cause of death, both globally and in Sweden, and accounts for approximately 15% of all deaths in the world (table 1) (1-6). During the past decades, age-standardized death rates due to CVD have declined, especially in high-income countries (4, 5). The cause of this decline is likely to be multifactorial, where improved primary and secondary prevention as well as improved treatments are key factors (7, 8). Nevertheless, every year some 0.3% of the population will suffer from an AMI and among them up to one in four will die from it.

Table 1: Mortality and incidence data on ischemic heart disease and acute myocardial infarction.

Region	Year	Total number of deaths by IHD or AMI	Percentage of all deaths caused by IHD or AMI	AMI / 100,000 inhabitants	Mortality < 28 - 30 days	Ref.
Global	2019	8.9 million	16%			(1)
Europe	< 2016	1.8 million	20%	172 - 3172[1]	5 – 15%	(4)
USA	2013 - 2017	110,000	14%	203	14 – 16%	(6, 9-11)
Sweden	2019	5,200	6%	311	11 – 25%	(12, 13)

[1] Lowest number from Andorra, highest number from Belarus

AMI = Acute Myocardial Infarction, IHD = Ischemic Heart Disease

1.3 DEFINITIONS

1.3.1 Acute Myocardial Infarction

An AMI is defined as the situation when there is clinical evidence of acute myocardial ischemia and acute myocardial injury due to a mismatch in the supply and demand of oxygen (figure 1) (14).

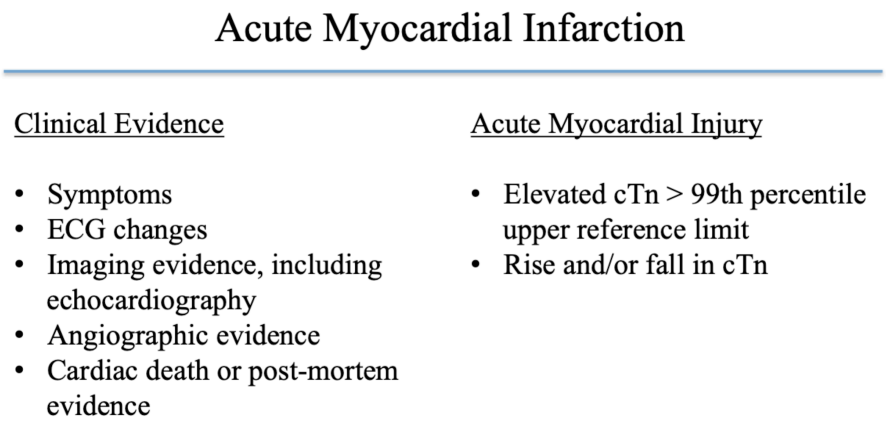


Figure 1: Definition of the term acute myocardial infarction, based on the fourth universal definition of myocardial infarction (14). cTn = cardiac troponin, ECG = electrocardiogram

Based on the underlying pathophysiology or clinical situation, the diagnosis of myocardial infarction can be further divided into subgroups (14):

Type 1: A ruptured or erosive plaque causes an occlusive or non-occlusive thrombus in a coronary vessel, leading to a myocardial infarction.

Type 2: An imbalance between oxygen supply and demand to the cardiac muscle, not caused by a ruptured plaque or thrombus. Other conditions, such as atherosclerosis, coronary spasm, or coronary dissection may, but do not have to, be present.

Type 3: Patients with symptoms and ECG-findings congruent with AMI who die before blood samples are obtained, or before a rise and/or fall in cardiac troponin (cTn) can be quantified.

Type 4a-c: Post-procedure myocardial infarction after percutaneous coronary intervention (PCI).

Type 5: Post-procedure myocardial infarction after coronary artery bypass graft (CABG) surgery.

In the clinical setting, ECG findings are of main importance to distinguish patients with ST-segment Elevation Myocardial Infarction (STEMI) from patients without such elevations, non-STEMI, as the importance of urgent reperfusion differs between the groups (15, 16).

1.3.2 Myocardial injury

Myocardial injury is defined as when cTn levels found in blood samples are higher than the 99th percentile upper reference levels (14). When there is a rise and/or fall in cTn, the myocardial injury is considered acute. Apart from AMI, there are numerous other conditions that can cause myocardial injury, both cardiac (e.g. myocarditis, heart failure) and non-cardiac (e.g. stroke, sepsis, kidney failure) (14, 17).

1.3.3 Coronary Artery Disease

Coronary Artery Disease (CAD) involves the build-up of atherosclerosis in coronary vessels. The disease entity itself is usually further divided into acute coronary syndrome (ACS), including myocardial infarction and unstable angina pectoris, or chronic coronary syndrome (18).

1.4 RISK FACTORS

1.4.1 The Framingham Heart Study and the INTERHEART study

Much of our knowledge today regarding risk factors for CVD comes from the Framingham Heart Study. Although accounting for about 50% of all deaths in the United States in the 1940s, little was understood at the time regarding risk factors (19). Between the years 1948 and 1952, the first original cohort, consisting of 5,209 (55% female) residents of Framingham, Massachusetts, without known CVD, was recruited (19, 20). Participants were invited for medical interviews and examinations, and then followed up biannually. Over the seven decades that have passed since the first inclusion, five additional cohorts (including offspring, spouses and general population reflecting ethnic diversity) have been recruited and more than 3,500 scientific papers have been published (20). Many of the findings from the Framingham cohort have also been supported by other studies. The INTERHEART study was an international case-control study (15,152 cases, 14,820 controls), aiming to investigate risk factors for myocardial infarction on a global perspective and also the population attributable risk (PAR) for each risk factor (21). The PAR can be seen as the fraction of a particular outcome that is attributed to a certain risk factor (22). Combined, nine risk factors accounted for over 90% of the PAR. Some of the main findings from the Framingham and INTERHEART studies regarding risk factors for CVD and AMI are summarized in table 2. Main risk factors include: hypertension, diabetes, hyperlipidemia, obesity, smoking, age, and physical inactivity (19, 21, 23).

1.4.2 Risk scores

Several tools have been developed to evaluate the risk of CVD. The European Society of Cardiology (ESC) recommends the use of SCORE (the Systematic COronary Risk Evaluation), which estimates the ten-year risk of fatal CVD (24, 25). The SCORE charts are based on twelve European cohort studies containing 2.7 million patient years of follow-up and 5,652 deaths due to coronary heart disease (25). Other risk scores include the Framingham Risk Score and the American Heart Association Heart Disease Risk Calculator.

Table 2: Two major studies determining risk factors for coronary vascular disease (Framingham Heart Study) and acute myocardial infarction (INTERHEART).

	Framingham Heart Study (23)		**INTERHEART (21)**	
Study design	Cohort		Case-Control	
Number of cases	610 (37% women)		15,152 (38% women)	
Number of participants	5,345 (53% women)		29,972 (32% women)	
Outcome	Coronary Vascular Disease		Acute Myocardial Infarction	
Inclusion site	Framingham, Massachusetts, USA		52 countries, all inhabited continents	
Publication year	1998		2004	
Risk reported	Relative Risk (95% CI) adjusted for all other variables in table		OR (99% CI) adjusted for age, sex and geographic region	
	Men	**Women**	**Men**	**Women**
Age	1.1 (1.0 – 1.1)	1.04 (1.0 – 1.1)		
Current smoking	1.7 (1.4 – 2.1)	1.5 (1.1 – 1.9)	3.1 (2.8 – 3.3)	2.9 (2.4 – 3.5)
Hypertension [1]	1.7 (1.3 – 2.2)	1.7 (1.2 – 2.5)	2.3 (2.1 – 2.5)	3.0 (2.6 – 3.4)
Diabetes	1.5 (1.1 – 2.1)	1.8 (1.2 -2.7)	2.7 (2.4 – 3.0)	4.3 (3.5 – 5.2)
Abdominal obesity			2.4 (2.0 – 2.5)	2.3 (1.9 – 2.7)
Physical activity			0.8 (0.7 – 0.9)	0.5 (0.4 – 0.6)
Psychosocial stress			2.6 (2.1 – 3.1)	2.5 (2.4 - 5.0)
Alcohol			0.9 (0.8 – 1.0)	0.4 (0.3 – 0.5)
LDL (> 160 mg/dL)	1.7 (1.4 – 2.2)	1.7 (1.2 -2.4)		
ApoB/ApoA1			3.8 (3.2 – 4.4)	4.4 (3.4 – 5.7)

[1] Framingham defined as ”hypertension I” as 140-159 mmHg in systolic blood pressure or 90-99 mmHg in diastolic blood pressure, compared with normotensives < 130/85 mmHg. INTERHEART defined hypertension by self-report.

CI = Confidence Interval, LDL = Low Density Lipoprotein, OR = Odds Ratio

1.5 NON-INVASIVE INVESTIGATIONS

1.5.1 Clinical presentation

Symptoms consistent with myocardial ischemia are of main importance in establishing the diagnosis myocardial infarction (14). Chest pain is the cardinal symptom and around 80% of patients with AMI present with chest pain (26). Other common symptoms include diaphoresis (≈ 45%), nausea (≈ 40%), and pain radiating to the left arm (≈ 30%) (26). In the TRAPID-AMI (high sensitive cardiac Troponin T assay for RAPID rule-out of Acute Myocardial Infarction) study, over 1,282 patients seeking emergency care for chest pain within six hours of symptom onset were included and interviewed by research staff (patients with ST-segment elevations were excluded) (27). Among included patients, 17% were diagnosed with AMI. Four independent variables were associated with AMI; pain radiating to the left or right arm or shoulder respectively, chest pressure, or symptoms worsened by physical activity (27). There also seem to be differences between male and female patients. One meta-analysis (n = 951,474) found that women with AMI were less likely to report chest pain than men (OR 0.63, 95% CI 0.59 – 0.68) (28), although other studies have found no such difference (26). However, women seem more likely to present with other symptoms such as nausea or neck pain (26, 28).

Although chest pain is a common complaint in AMI patients, most patients seeking emergency care for chest pain do not have acute coronary syndrome (27), and it is thus important to have non-objective tools when assessing these patients.

1.5.2 Cardiac troponin

Cardiac troponin is a protein complex involved in the interaction between actin and myosin in heart muscle cells (14). When such cells are injured, cTn is released into the blood stream and can be detected and quantified in blood samples. For the detection of myocardial injury, high-sensitivity assays are recommended, as these assays have a higher diagnostic accuracy in the early detection of AMI (29). It is important to stress that cTn should be interpreted in combination with the clinical presentation and with other findings as all patients with elevated cTn levels do not have AMI.

1.5.3 The ECG

1.5.3.1 A brief history

The knowledge that electrical currents can be detected from skeletal muscle dates back to the late 1700s, and the first human recording of cardiac electrical activity was published by Dr. Waller in 1882 (30). Inspired by Dr. Waller, Dr. Einthoven developed the first three-lead electrocardiogram in 1901 for which he was later awarded the Nobel Prize in Physiology or Medicine. Further milestones in the development of modern ECG machines were the central terminal (Dr. Wilson, 1934-38) and the augmented unipolar leads (Dr. Goldberger, 1942). In

1954 the American Heart Association published their recommendations on the 12-lead ECG as we know it today (30).

1.5.3.2 The normal ECG

The standard 12-lead ECG records differences in electrical potential between defined sites on the body surface (figures 2A and B) (31). More specifically, it reflects the progression of the trans-membrane difference in action potential of the heart muscle cells over the cardiac cycle and the ECG thus describes the electrical events of cardiac depolarization and repolarization. The variations of potential are caused mainly by the movement of K^+, Na^+ and Ca^{++} across the cell membrane (32). This cycle of inward and outward movement of electrolytes is in part dependent on adenosine triphosphate. The signals recorded from the electrodes are then filtered to reduce disturbances, e.g. from respiration, muscle artifacts, and movement. The result is a graphical presentation, consisting of a series of complexes depicting the electrical activity in the heart viewed from twelve different sites (figure 2C). The different positive and negative deflections are noted with the letters PQRST (figure 2D). A wave of depolarization moving toward, or a wave of repolarization moving away from the positive electrode will generate a positive wave on the ECG, and the magnitude of the wave depends on the mass of cardiac tissue undergoing depolarization or repolarization (32).

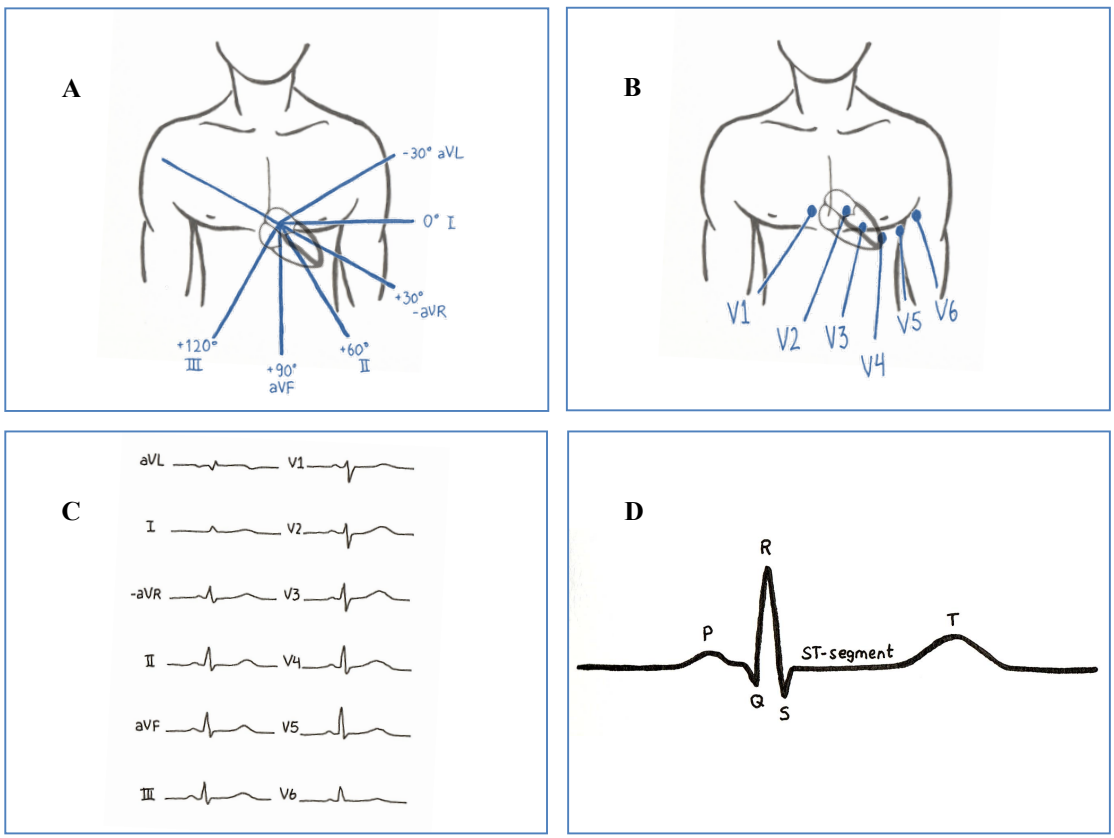


Figure 2: Illustrations of A) Bipolar leads of Einthoven and unipolar leads of Goldberger, acquired by electrode placement on the extremities, B) the unipolar precordial leads, C) a 12-lead ECG and D) a single PQRST- complex.

1.5.3.3 Interpretation of the ECG

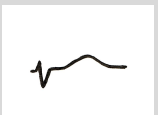
In the clinical setting, the ECG is possibly the most commonly used diagnostic instrument as it is easy to acquire, non-invasive, and provides a wide range of information. In order to facilitate and standardize interpretations and readings of ECGs, the American Heart Association, The American College of Cardiology Foundation and the Heart Rhythm Foundation published a six-part series of recommendations (31, 33-37). Interpretation of an ECG is an integral part of cardiologist training, but experienced cardiologists cannot read all ECGs.

In many cases, a computerized interpretation (CIE) is provided, and the ECG is then over-read by other professionals such as nurses, emergency medical services, or specialist physicians in other areas of medicine. The role of CIE is appealing as it facilitates the readings for the physician, e.g. by providing measurements of basic parameters such as heart rate, but CIE is not always accurate. Also, conducting and comparing studies on CIE usually involve the use expert readers such as experienced cardiologists, who sometimes might disagree, as gold standard. In the setting of STEMI, three different CIE algorithms were evaluated for the identification of a culprit artery. The sensitivities ranged from 62 - 69% and specificities from 89 - 95% (38). The general recommendations remain that all CIE are over-read by an experienced ECG reader (39).

1.5.3.4 ECG findings in or after AMI

Acute myocardial ischemia can cause different types of ECG disturbances. When hypoxia occurs to the heart muscle cell, adenosine triphosphate is reduced and extracellular potassium is increased. This causes disturbances in the movement of ions across the cell membrane and can lead to a variety of changes, such as changes in heart rhythm, conduction blocks and also changes in the morphology of the ST-segment. The definitions of some of the most common ECG findings during or after a myocardial infarction are found in table 3.

Table 3: Definitions and pathophysiology of ECG findings during or after a myocardial infarction.

	Definition	Pathophysiology	Reference
ST-segment elevation 	New, or presumed new, ST-elevations measured at the J-point (the onset of the ST-segment) of at least 1 mm in two contiguous leads, with the exception of V2-V3 where ≥ 2.5 mm is required in men < 40 years, ≥ 2 mm in men ≥ 40 years and ≥ 1.5 mm in women, in the absence of signs of left ventricular hypertrophy or left ventricular bundle branch block.	Generally indicative of a transmural ischemia. The damaged region causes an area of depolarization. Vectors occur moving away from the overlying electrode between the damaged and healthy areas when the healthy areas are repolarized, causing a downward shift of the baseline.	(14, 15, 32, 37)
ST-segment depression 	New, or presumed new, horizontal or downward-sloping ST-depressions of ≥ 0.5 mm in two contiguous leads.	Generally indicative of a subendocardial ischemia. When the ventricle is fully repolarized, vectors between the damaged and healthy areas occur, causing an upward shift of the baseline.	(14, 32, 37)
T-wave changes 	New inverted T-waves of ≥ 1 mm in two contiguous leads where the R-wave is prominent or the R/S-ratio > 1.	In the setting of a subendocardial infarction, the wave of repolarization may change from the normal subendocardial to subepicardial direction and instead may become subepicardial to subendocardial, thus reversing the direction of the T-wave.	(14, 32)
Pathologic Q-waves 	Any Q-waves in V2-V3 > 20 ms or QS complex in V2-V3, or Q-waves ≥ 30 ms or QS-complex in leads aVL, I, II, aVF or V4-V6 in any two leads of a contiguous lead grouping.	In early depolarization, the net electrical forces move away from the overlying electrode. Correlated to size of infarction.	(14, 40)
Pathologic R-wave progression 	Poor R-wave progression: R in V3 ≤ 3 mm. Reversed R-wave progression: R-wave in V2 < V1, V3 < V2, V4 < V3 or V4 ≤ 3 mm.	Depolarization forces reduced in magnitude.	(41)

1.5.3.5 The significance of Q-waves and pathologic R-wave progression

Various studies have demonstrated that for patients with STEMI, the presence of Q-waves on the presenting ECG is associated with a poor prognosis (42, 43). One systematic review (n = 20,842) found that for STEMI-patients presenting with Q-waves, the risk of death within 30 days was about twice as high compared to patients without Q-waves (RR 2.2, 95% CI 1.3 – 3.6) (42). The presence of Q-waves is also associated with infarct size (44, 45). There is a possibility that Q-waves can regress after reperfusion and over time. One study among 761 STEMI-patients found a reduction the number of Q-waves between post-PCI and discharge for 22% of the patients (46). In the same study, patients with persistent Q-waves had an almost five-fold increased risk of heart failure or death within one year compared to patients without Q-waves.

Pathologic R-wave progression signifies a decreased magnitude of the R-wave in the precordial leads, and has been associated with anterior myocardial infarctions. It has also been associated with heart failure, and patients with prior anterior AMI who have a pathologic R-wave progression have a lower left ventricular ejection fraction (LVEF) on echocardiography than patients with normal R-wave progression (average LVEF 46% vs. 55%, $p < 0.01$) (47). For patients without a known myocardial infarction, the use of pathologic R-waves for the identification of patients with a prior silent myocardial infarction has, however, been questioned. One study showed that only around 30% of 122 patients referred to pharmacological stress tests and who had a pathologic R-wave progression had evidence of anterior ischemia, which was not significantly different from patients with normal R-wave progressions (48).

1.5.3.6 The role of the ECG in predicting sudden cardiac death

The use of pathologic findings on resting ECGs in the prediction of sudden cardiac death (SCD) was explored in the community-based Oregon Sudden Unexpected Death Study. The study was a multi-center case-control study including 522 cases with out-of-hospital cardiac arrests (including survivors of cardiac arrest) and 736 controls. An ECG score consisting of eight ECG variables (heart rate, QRS-duration, corrected QT-time, T-peak-Tend duration, QRS-T angle > 90%, delayed QRS transition zone, left ventricular hypertrophy and R-wave peak time) was analyzed and the authors concluded that, after adjusting for clinical factors and LVEF, a higher ECG score was associated with a higher risk of cardiac arrest. For patients with an ECG score > 4, the OR was 21.2 (95% CI 9.4 – 47.7, $p < 0.001$) (49).

More advanced three-dimensional ECG markers on global electric heterogeneity based on standard 12-lead ECGs but measured by computer software have been found to be independently associated with the risk of SCD. Two large prospective American cohorts; ARIC (the Atherosclerosis Risk in Communities, n = 15,792) and CHS (the Cardiovascular Health Study, n = 5,888) were merged. Markers of global electric heterogeneity were

independently associated with an increased risk of SCD in the general population and inclusion of such parameters to clinical risk scores improved risk prediction (50).

In patients with prior myocardial infarction, the use of the Selvester QRS-scores (based on amplitudes, durations and ratios of the Q, R, and S waves in ten out of twelve ECG leads) has been studied in the SCD-HeFT (Sudden Cardiac Death – Heart Failure Trial) and the MADIT II (Multicenter Automatic Defibrillator Implantation Trial) (51, 52). In the SCD-HeFT, patients with a normal QRS-score had a significantly lower risk of experiencing malignant ventricular arrhythmias, HR 0.52 (95% CI 0.31 – 0.88), whereas the results in the MADIT II were non-significant. The authors speculate that the lower LVEF cutoff value for inclusion in MADIT II could contribute to this finding.

Other ECG-based measurements, including bundle branch blocks and QRS-duration on resting ECG, electrophysiological studies, signal averaged ECG, T-wave alternans and heart rate variability on Holter ECG, have also been explored for the prediction of SCD in patients with myocardial infarction (53).

1.5.4 Echocardiography

1.5.4.1 A brief history

The discovery of the piezoelectric effect (the effect that kinetic or mechanical energy can be converted to electrical energy) is attributed to the Curie brothers during the 1880s (54). Clinical echocardiography started in 1953 in Lund, Sweden, by Edler and Hertz, who then, by the use of an ultrasound machine connected to a camera, recorded the first non-invasive picture of a moving structure in the heart (55). Over the decades that have since passed, the technique has been vastly improved. Some of the milestones are the development of 2D echocardiography in the 1960s and Doppler echocardiography in the 1970s (54). Digital storing of information, transesophageal echocardiography, contrast enhancing agents and 3D echocardiography have further expanded the clinical use of echocardiography.

1.5.4.2 Ejection fraction

Left ventricular ejection fraction is defined as the difference between the left ventricular end-diastolic volume and end-systolic volume, divided by the end-diastolic volume (56). The recommended methods for the echocardiographic measurement of LVEF are either 3D echocardiography or the Simpson biplane method of discs using 2D. LVEF can be seen as a method to measure left ventricular global function. Echocardiographic reference values for LVEF are 54 - 74% for women and 52 - 72% for men (56).

The ESC guidelines on heart failure define heart failure as a clinical diagnosis based on symptoms (e.g. shortness of breath, ankle swelling) and signs (e.g. pulmonary crackles and edema) caused by a structural or functional cardiac abnormality that leads to decreased cardiac output and/or increased filling pressures at rest or during exercise (57). The second criteria for the diagnosis is based on LVEF; where LVEF < 40% is referred to as heart failure

with reduced LVEF and LVEF > 50% referred to as heart failure with preserved LVEF. For patients with heart failure and LVEF 40-49% the term heart failure with mid-range LVEF is used.

For patients with myocardial infarction, many studies have found a clear association between low LVEF and a poor prognosis (58, 59). Also, for patients with STEMI, shorter delay times between presentation and reperfusion therapy is associated with higher LVEF at follow-up (60, 61).

1.5.4.3 Stunning, hibernation, and stress echocardiography

Echocardiography is recommended during hospital stay for patients with AMI (15, 16, 62). Left and right ventricular global and regional functions are assessed and mechanical complications and thrombus formation can be ruled out. In the case of suspected, but not confirmed, acute coronary syndrome alternative diagnoses such as pericardial effusion or aortic dissection may be identified.

The reaction of the left ventricle to the ischemic situation will in large depend on the extent and duration of the ischemia. If the ischemia is severe and prolonged, necrosis of the affected area of the left ventricle will occur and the necrotic myocardium will not recover. If however the duration of the ischemic episode is transient, the affected segments of the ventricle that initially show impaired contractile function may recover over time. This is referred to as myocardial *stunning* (63, 64). If there are repeated episodes of stunning, or a more chronic situation with reduced perfusion, metabolic adaptations will occur in the heart muscle cells. Although still viable, these cells may not contract during rest but can still recover after reperfusion. This phenomenon is referred to as *hibernation* (63, 64). In the clinical setting it can be of importance to differentiate hibernating or stunned regions from necrotic ones. Stress echocardiography can be used to detect myocardial viability. Using a low dose of dobutamine as a continuous infusion, akinetic or hypokinetic segments may improve in contraction implying viability and that a contractile reserve exists (63, 64).

1.6 EARLY REVASCULARIZATION FOR PATIENTS WITH STEMI

Early reperfusion treatment for patients with STEMI is associated with decreased mortality. A large American cohort study, based on registry data on more than 29,000 STEMI patients treated by PCI within six hours of presentation between 1999 and 2002, found that a door-to-balloon time longer than 90 minutes was associated with an increased risk of in-hospital death, HR 1.4 (95% CI 1.2 – 1.6) (65). These findings were congruent with what was reported from the GUSTO-IIb study (Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes), where the risk of death within 30 days increased 1.6 times (95% CI 1.1 – 2.3, p = 0.008) per 15 minutes delay time measured as the time from enrollment in the study to balloon inflation (66). Similarly, a Swedish registry-based cohort study investigated the association between the time from first medical contact (FMC) to PCI versus death within one year among more than 13,000 patients treated between 2003 and 2009. In this study, a hazard ratio for all cause mortality of 1.26 (95% CI 1.03-1.55) was

found comparing delay times 61-90 minutes to < 30 minutes, and higher hazard ratios with even longer delay times (67).

1.7 TIME MANAGEMENT AND TIME COMPONENTS

1.7.1 Time targets and components

Due to the benefits of early or immediate reperfusion therapy for patients with STEMI, current international guidelines advocate rapid identification and primary PCI for these patients (15). The time target for a diagnosis of STEMI, defined as when the ECG is interpreted and ST-elevations or equivalents are confirmed, is set within ten minutes from ambulance arrival. For patients who arrive by emergency medical services (EMS) or for self-presenters to non-PCI-capable hospitals, the goal is then primary PCI within 90 minutes, if such therapy is available (15). For self-presenters at PCI-capable hospitals, the goal is primary PCI within 60 minutes from STEMI diagnosis. The total ischemic time can thus be divided into several time components for benchmarking compared to international guidelines and in order to identify possible areas of improvement (figure 3).

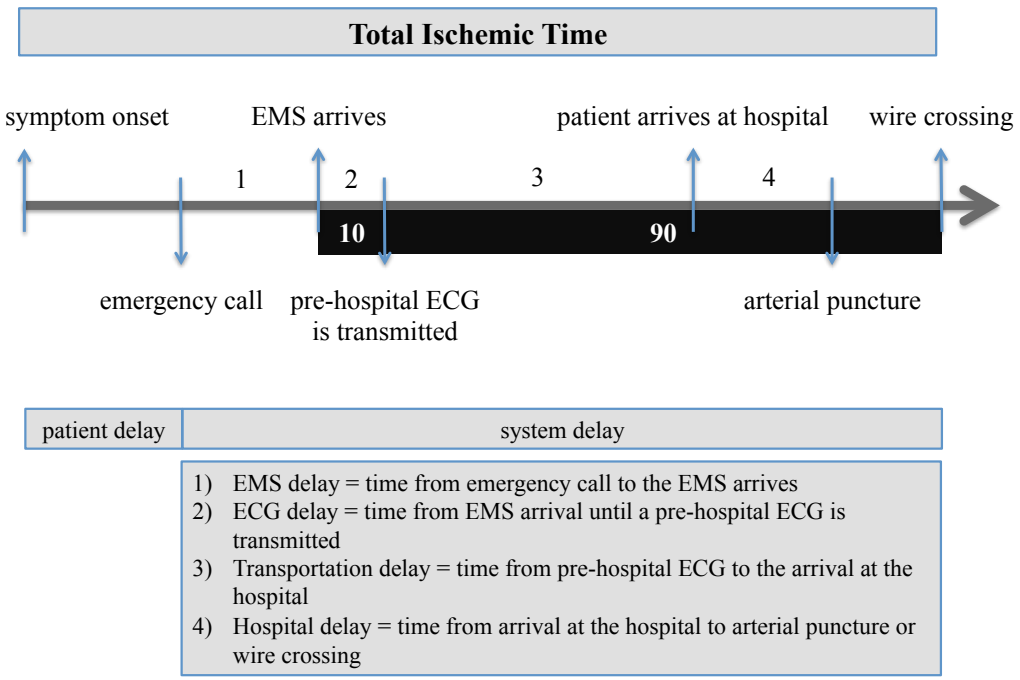


Figure 3: An overview of delay times for patients with STEMI arriving by EMS, including both pre-hospital and in-hospital delay times. Black boxes denote target delay times in minutes according to the European Society of Cardiology (15). ECG = Electrocardiogram, EMS = Emergency Medical Services.

1.7.2 Pre-hospital alerts

Various alert systems have been developed in order to reduce ischemic time for patients with STEMI, and the guidelines recommend implementation of efficient networks between hospitals and EMS services (15, 68). For patients with STEMI, it has been shown that contacting EMS yields the shortest total ischemic times, compared to self-presentation in the emergency department or first contacting primary care (69). The use of pre-hospital ECGs, with the possibility of bypassing the emergency department and referring the patient directly from the ambulance to the catheterization laboratory (CL), has been shown to be associated with shorter delay times (70-73). Through such systems, EMS personnel acquire a pre-hospital ECG and the ECG is then either transferred wirelessly to a receiving hospital or interpreted by paramedics or EMS physicians on site. If the symptoms and the ECG are consistent with STEMI, the CL can immediately be activated and necessary preparations can be done during transport. In many systems, the patient does not have to stop in the emergency department but can be taken directly to the CL.

There is a trend towards reductions in delay times for STEMI patients. The national quality registry SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Treatment) reported a reduction in median total ischemic time from 211 minutes in 2003-2004 to 190 minutes in 2013-2014, $p < 0.001$ (74). A nation-wide Polish registry also noted a similar decrease in total ischemic time between 2006 and 2013 (268 vs. 230 minutes, $p < 0.001$) and door-to-balloon time (46 vs. 42 minutes, $p < 0.001$) (75).

1.7.3 Gender differences in delay time

Various components of the total ischemic time have been found to be longer for women than for men. Based on SWEDEHEART data from 2004 - 2006 (n = 14,380), the median total ischemic time was 30 minutes longer for women than for men (3h 30 min vs. 3h, $p < 0.001$) and the median time from first ECG to angiography was five minutes longer for women (76). Similar numbers have been reported from the ISACS-TC (International Survey of Acute Coronary Syndromes in Translational Countries (n = 6,022) where women had a 30 minute longer delay time between symptom onset and hospital presentation, but similar door-to-needle and door-to-balloon time, compared to men (77). Also, a Danish study found that female gender was an independent predictor of patient delay times over two hours (78).

In an Australian cohort of 735 STEMI patients, female patients had a median door-to-balloon time 16 minutes longer than men (88 vs. 72 minutes, $p = 0.001$) (79). Also, in some populations female gender seems to be associated with a lower chance of achieving the target of reperfusion within 90 minutes. One study among STEMI patients in New York (n = 245) found that female gender had an OR of 0.2 (95% CI 0.1 – 0.6, $p = 0.003$) of reperfusion within 90 minutes compared to men (80).

1.8 ACCURACY OF STEMI DIAGNOSIS

It is important to assess the rapid management of patients with suspected STEMI in combination with accuracy of diagnosis. Coronary angiography is an invasive diagnostic procedure that comes with both a cost and risk of complications. The rate of false-positive CL activations for patients with suspected STEMI seems to be between around ten and up to 50% (table 4). Direct comparisons between studies are difficult, as different populations and different measures of outcome have been used. A summary of some of the main studies aiming to find the rate of false-positive catheterization laboratory activations for suspected STEMI is found in table 4.

Table 4: Studies on the accuracy of diagnosis among patients with suspected STEMI and for whom the catheterization laboratory was notified.

Study	n	Where was the patient when diagnosed?	Who activated the CL?	Outcome and rate of false-positive activations
Larson et al., JAMA 2007 (81)	1,335	ED or community hospital	ED Physician (Cardiology consultation available)	No culprit lesion and negative biomarker: 9% (95% CI: 8-11%)
Youngquist et al., Academic Emerg Med 2008 (82)	56	Field: 41% ED: 59%	Field: ECG interpretation computerized. ED: ED physicians	No culprit lesion or negative biomarker and alternative cause of ST-elevation on ECG: Field-activations: 39%, ED-activations: 9%
Zeymer et al., Resuscitation 2008 (83)	2,326	Ambulance	EMS Physician	Discharge diagnosis other than STEMI: 10%
Barge-Caballero et al., Rev Esp Cardiol 2010 (84)	1,662	Out-of-hospital: 16% ED: 84%	Out-of-hospital: Physicians in emergency unit ED: ED physicians	No culprit lesion: 7% (95% CI: 7-9%)
Garvey et al., Circulation 2012 (85)	3,973	EMS-activations: 29%	Out-of-hospital: paramedic ED: ED physicians	CL cancellation due to ECG reinterpretation or patient not suitable for catheterization: EMS: 25%, Whole group: 15%
McCabe et al., Arch Intern Med 2012 (86)	411	ED	ED Physician (Cardiology consultation available)	No culprit artery or, in patients without angiography, 2/3 of negative biomarker/ECG/symptoms: 33%

Table 4 continued on following page.

Table 4 continued.

Study	n	Where was the patient when diagnosed?	Who activated the CL?	Outcome and rate of false-positive activations
Nfor et al., J of Emerg Med 2012 (87)	489	ED	ED physician	No culprit lesion: 11% (95% CI: 8 – 14%)
Barnes et al., Am J Managed Care 2013 (88)	717	Out-of-hospital: 33-52%	EMS or ED	Interventional cardiologist determined that patient did not need emergent transfer: 28%
Rasmussen et al., Heart 2014 (89)	919	Ambulance or helicopter	Physician on call in hospital	No STEMI diagnosis (ECG and culprit lesion: 16%
Tolles et al., Prehosp Disaster Med 2020 (90)	1877	Ambulance	Receiving ED physician	No PCI or CABG during hospital stay: 60% before 2015, 51% after 2015

CABG = Coronary Artery Bypass Surgery, CI = Confidence Interval, CL = Catheterization Laboratory, ECG = Electrocardiogram, ED = Emergency Department, EMS = Emergency Medical System, PCI = Percutaneous Coronary Intervention, STEMI = ST-segment Elevation Myocardial Infarction

1.9 MORBIDITY AND MORTALITY AFTER AN ACUTE MYOCARDIAL INFARCTION

1.9.1 Heart failure

The development of heart failure after an AMI remains a main concern despite vast medical advances over the past decades. Swedish registry data among almost 200,000 hospital admissions for AMI between 1996 and 2008 have been used to study the incidence of heart failure among AMI patients, and a decline from 46% to 28% has been observed (91). In the same study, only around 30% of AMI patients had an LVEF ≥ 50% in 2008. The incidence of heart failure after AMI has also been studied using the Danish National Patient Registry. Among around 79,000 patients recorded between 2000 – 2009, 21% developed heart failure during hospital stay or within a year after the AMI, and patients with heart failure had an approximately three-fold increased risk of death within one year (92).

Women seem to have an increased risk of heart failure after an AMI compared to men. In the ISACS-TC study, women had a 25% of developing de novo heart failure compared to 20% in men (93).

1.9.2 Sudden Cardiac Death

Sudden cardiac death is defined as a sudden, unexpected death due to a cardiac cause within one hour of symptom onset (94, 95). Approximately 25% of all deaths due to cardiovascular diseases are SCD (95). In the setting of myocardial infarction, reduced LVEF has repeatedly been shown to be associated with an increased risk of SCD, and the risk of SCD is highest early after a myocardial infarction. In the VALIANT (Valsartan In Acute Myocardial Infarction Trial) study, 7% of 14,703 patients with an LVEF ≤ 40% experienced SCD or were resuscitated after a cardiac arrest during a follow-up period of two years (96). In the trial, the median time to event was 180 days and 19% of all events occurred within the first month. The risk was highest for those patients who had LVEF ≤ 30%, figure 4 (96).

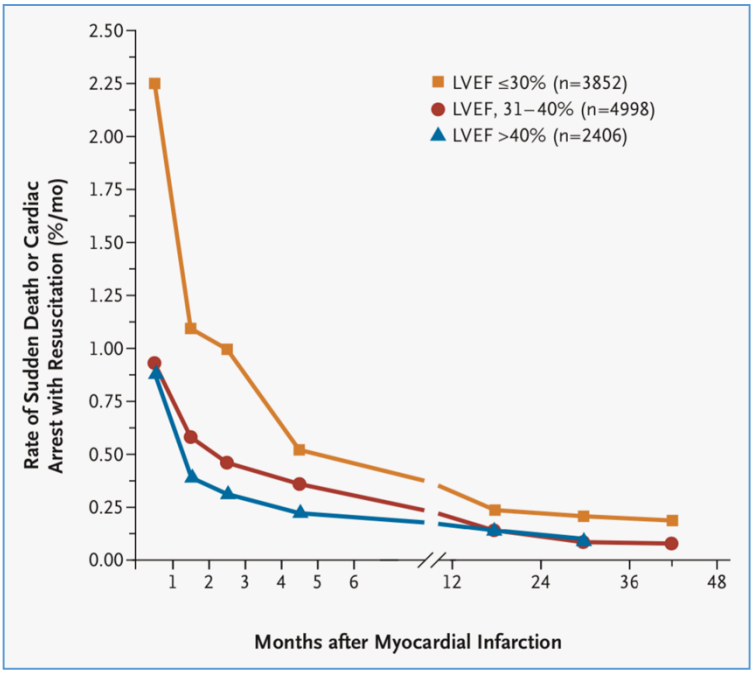


Figure 4: Rate of sudden cardiac death or cardiac arrest vs. time after AMI, by groups of ejection fraction. Reproduced with permission from Solomon SD, Zelenkofske S, McMurray JJ, Finn PV, Velazquez E, Ertl G, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. The New England journal of medicine. 2005;352(25):2581-8. Copyright Massachusetts Medical Society.

1.10 THE IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD)

1.10.1 The evolution of the ICD

The first ICD was implanted at the Johns Hopkins Hospital in Maryland, USA, by Dr. Mirowsky and his team in 1980 (97). The device consisted of an electrode placed in the vena cava superior near the right atrium and a patch sutured on to the cardiac apex. Both electrodes were then connected to a titanium-encased pulse generator placed in the abdomen. While the original ICDs occupied a volume of 145 mL and weighed 250 g, modern ICD devices are in the 40 mL range and weigh around 60-70 grams.

1.10.2 ICD in secondary prevention

For patients who have experienced malignant ventricular arrhythmias, the first major trial to demonstrate the benefit of an ICD over pharmacological antiarrhythmic therapy was the AVID (Antiarrhythmic Versus Implantable Defibrillator) trial (98). In AVID, 1,013 patients with ventricular fibrillation or sustained ventricular tachycardia were randomized to receive either an ICD or antiarrhythmic medication. The study showed a significant relative risk reduction in all-cause mortality of approximately 30% favoring ICD treatment, and the study was therefore terminated early. Two other, smaller trials, CIDS (Canadian Implantable Defibrillator Study) and CASH (Cardiac Arrest Study Hamburg), showed similar results but did not reach statistical significance (table 5). It was argued that, since the AVID was terminated early the benefits of ICD treatment might be overestimated. The three studies have later been pooled in a meta-analysis, comparing ICD treatment to amiodarone (99). The results of the meta-analysis were consistent with the separate studies and found a HR of 0.72 (95% CI 0.60 – 0.87), $p < 0.001$ for all-cause mortality and HR 0.5 (0.37 – 0.57), $p < 0.0001$ for death caused by arrhythmia.

Table 5: Summary of three major studies on the use of implantable defibrillators as secondary prevention

Study	n	Inclusion criteria	Study groups	Relative Risk Reduction
AVID, 1997 (98)	1,013	Near-fatal VF, sustained VT with syncope or sustained VT with LVEF ≤ 40% and symptoms	ICD vs. antiarrhythmic drugs (mainly amiodarone)	31%, $p < 0.02$
CIDS, 2000 (100)	659	Documented VF, cardiac arrest requiring defibrillation, sustained VT with syncope, sustained VT > 150 beats/minutes with LVEF ≤ 35% and symptoms, syncope with evidence of VT	ICD vs. amiodarone	20%, $p = 0.142$
CASH, 2000 (101)	288	Resuscitation from cardiac arrest, not within 72 from an acute myocardial infarction, electrolyte disturbances, cardiac surgery or pro-arrhythmic drugs	ICD vs. amiodarone vs. metoprolol	23%, $p = 0.081$

AVID = Antiarrhythmic Versus Implantable Defibrillator, CASH = Cardiac Arrest Study Hamburg, CIDS = Canadian Implantable Defibrillator Study, ICD = Implantable Cardioverter Defibrillator, LVEF = Left Ventricular Ejection Fraction, VF = Ventricular Fibrillation, VT = Ventricular Tachycardia

1.10.3 ICD in primary prevention

Several clinical trials have demonstrated the benefit of ICD treatment to patients with ischemic heart disease and reduced LVEF (102-106), table 6. The relative risk reduction of all-cause mortality is approximately 30 – 50% by ICD treatment. The MADIT (Multicenter Automatic Defibrillator Implantation Trial) was the first major trial for the primary prevention of SCD by ICD. Patients with prior myocardial infarction, LVEF ≤ 35%, non-sustained ventricular tachycardia and positive electrophysiological provocation were randomized to receive either an ICD or pharmacological antiarrhythmic treatment (mainly amiodarone). During an average follow-up period of 27 months, the risk of death by any cause was significantly lower in the ICD group, HR 0.46 ($p = 0.009$). Later, the MADIT II and the SCD-HeFT (Sudden Cardiac Death – Heart Failure Trial) also confirmed the benefit of ICD in patients with patients with prior myocardial infarction and LVEF ≤ 30% and ≤ 35% respectively but without the need of electrophysiological studies (104, 105).

For patients with AMI, the timing of ICD implantation is of great importance. All patients included in the MADIT I and II studies had experienced an AMI prior to enrollment in the studies. In the first MADIT study, more than six months had passed between the AMI and enrollment for over 75% of the study population, and in the MADIT II study the same was true for over 87% of the participants. The DINAMIT (Defibrillator IN Acute Myocardial Infarction Trial) and IRIS (Immediate Risk-stratification Improves Survival) trials were both large randomized controlled trials studying the effect of ICDs implanted early after a myocardial infarction. In the DINAMIT study patients were enrolled within 5 – 31 days after an AMI and in the IRIS within 4 – 40 days. Both trials failed to show any benefit in all cause mortality (table 6).

Current international guidelines therefore recommend that the decision of ICD implantation be delayed until 6-12 weeks after the AMI, after re-assessment of LVEF is performed (15, 95). According to the ESC guidelines for the management of STEMI patients, ICD treatment is recommended to patients with symptomatic heart failure and who are expected to live for at least one year with good functional status, if the LVEF is ≤ 35% despite optimal medical treatment for at least three months and if at least six weeks have passed since the AMI (15). This is stated as a class I level A recommendation, and it is based mainly on evidence from the MADIT II and SCD-HeFT trials. As seen in figure 4, the risk of SCD is highest during the early phase after an AMI, but, as seen in the DINAMIT and IRIS trials, implantation of an ICD within a month from the AMI does not reduce all-cause mortality for patients with reduced LVEF. Other parameters than LVEF are therefore of high interest to find in order to improve the prognosis for these patients, and to identify at an earlier stage what patients might benefit from the early implantation of an ICD.

Table 6: Summary of major randomized controlled trials on the use of implantable cardioverter defibrillators as primary prevention.

Study	n	Inclusion criteria	Study groups	HR (95% CI), for all cause mortality
MADIT, 1996 (102)	196	AMI > 3 weeks prior, LVEF ≤ 35%, NSVT, positive EP-study	ICD vs. conventional	0.46 (0.26 – 0.82)
MUSTT, 1999 (103)	704	CAD, LVEF ≤ 40%, NSVT, positive EP-study	Antiarrhythmic drugs ± ICD vs. no antiarrhythmic drugs	0.45 (0.32 – 0.63) [1]
MADIT II, 2002 (104)	1,232	AMI > 1 month prior, LVEF ≤ 30%	ICD vs. conventional	0.69 (0.51 – 0.93)
SCD-HeFT, 2005 (105)	2,521 (52% ischemic)	NYHA II-III, LVEF ≤ 35%	ICD vs. amiodarone vs. conventional	0.79 (0.60 – 1.04) [2]
COMPANION, 2004 (106)	1,520 (55% ischemic)	NYHA III-IV, LVEF ≤ 35%, QRS ≥ 120 ms, PQ > 150 ms	CRT-D, vs. CRT-P, vs. conventional	0.64 (0.48 – 0.86) [3]
DINAMIT, 2004 (107)	674	AMI within 6 – 40 days, LVEF ≤ 35%, depressed heart rate variation or 80 beats/min	ICD vs. conventional	1.08 (0.76 – 1.55)
IRIS, 2009 (108)	898	AMI within 31 days, LVEF ≤ 40% and heart rate > 90 beats/min or NSVT on Holter ECG	ICD vs. conventional	1.04 (0.81 – 1.35)

[1] Defibrillator vs. no antiarrhythmic drugs

[2] Patients with ischemic cardiomyopathy

[3] Defibrillator vs. conventional group

AMI = Acute Myocardial Infarction, CAD = Coronary Artery Disease, CI = Confidence Interval, COMPANION = Comparison of Medical therapy, Pacing and Defibrillation in Heart Failure, CRT-D/P = Cardiac Resynchronization Therapy – Defibrillator/Pacemaker, DINAMIT = Defibrillator IN Acute Myocardial Infarction Trial, EP = Electrophysiological, HR = Hazard Ratio, ICD = Implantable Cardioverter Defibrillator, IRIS = Immediate Risk-stratification Improves survival, LVEF = Ejection Fraction, MADIT = Multicenter Automatic Defibrillator Implantation Trial, MUSTT = Multicenter Unsustained Tachycardia Trial, NSVT = Non-Sustained Ventricular Tachycardia, NYHA = New York Heart Association, SCD-HeFT = Sudden Cardiac Death – Heart Failure Trial,

2 AIMS

The overall goal of this thesis was to investigate the use of simple diagnostic and clinically available measurements on ECG and echocardiography that could improve the prognosis for patients with acute myocardial infarction. With fast and correct management of patients with AMI, the risk of heart failure could be reduced. And if, despite all efforts, heart failure does occur, with faster identification of ICD candidates, the risk of death might be reduced. More specifically, the following aims were set:

STUDY I

To study the rate of false-positive catheterization laboratory activations based on pre-hospital ECGs, and to study the delay time intervals for patients with suspected STEMI.

STUDY II

To study the adherence to the target of acquiring a pre-hospital ECG within ten minutes from ambulance arrival, and to study gender differences in delay time intervals for patients with STEMI.

STUDY III

Among patients with a reduced left ventricular ejection fraction after an acute myocardial infarction: to study if simple measurements on stress echocardiography could predict improvement of ejection fraction over time.

STUDY IV

For the early identification of ICD candidates: to study the predictive value of ECG findings before discharge for patients with an acute myocardial infarction.

3 MATERIAL AND METHODS

3.1 STUDIES I AND II

3.1.1 The chain of care for patients with suspected STEMI

EMS personnel first assessed patients who had contacted EMS and for whom an ambulance had been dispatched. The investigating hospital was based in Stockholm, Sweden, and served a catchment area of approximately 0.5 million inhabitants. Approximately 70 ambulances, staffed by one paramedic and one specialist nurse, circulated the area. Pre-hospital ECGs were acquired at the discretion of EMS staff for patients with chest pain, but also with other symptoms such as syncope or palpitations. The pre-hospital ECG was acquired by the use of a portable device (MobiMed, Ortivus, Sweden) and the ECG was transmitted digitally and wirelessly to the investigating hospital. At the investigating hospital, each ECG was reviewed by a cardiologist or cardiology resident who contacted the ambulance by telephone. If the symptoms and ECG signs were consistent with STEMI, the cardiologist immediately contacted the CL and a pre-hospital STEMI alert was initiated.

3.1.2 Time Definitions, Sources, and Intervals

Measurements of the delay time intervals for patients with suspected STEMI were analyzed in studies I and II. Figure 3 and table 7 summarize the definitions used in the studies.

Table 7: Time definitions and data sources used in studies I and II.

	Definition	Data acquired from
Symptom onset	The time when the patient first experienced symptoms consistent with STEMI	Medical charts
Emergency call	The time when the patient contacted emergency services	Ambulance charts
Arrival of EMS	The time when the ambulance arrived at the patient's location	Ambulance charts
Pre-hospital ECG	The time when the pre-hospital ECG was transmitted to the investigating hospital	Database for pre-hospital ECG
Arrival at the hospital	The time when the ambulance arrived at the hospital	Ambulance charts
Arterial Puncture	The time of arterial puncture in the CL	SWEDEHEART

CL = Catheterization Laboratory, ECG = Electrocardiogram, EMS = Emergency Medical Services, STEMI = ST-segment Elevation Myocardial Infarction, SWEDEHEART = Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Treatment

For the time interval analyses, the differences between the various time components were used. Due to feedback from reviewers and readers after the publication of study I, the terminology was slightly changed in study II. A summary of time interval definitions is found in table 8.

Table 8: Time interval definitions used in studies I and II.

Study I	Study II	Definition
	Patient delay	Symptom onset to emergency call
EMS delay	Response time	Emergency call to the arrival of EMS
FMC to ECG	ECG time	Arrival of EMS to the transmission of a pre-hospital ECG
ECG to door	Transport time	Pre-hospital ECG to the arrival at the hospital
Door to needle	Hospital time	Arrival at the hospital to arterial puncture
ECG = electrocardiogram, EMS = Emergency Medical Services, FMC = First Medical Contact		

3.1.3 STEMI diagnosis

The definition of a true STEMI in studies I and II were based on the entry in SWEDEHEART. SWEDEHEART is a level one national quality registry and it includes information on patients treated for acute myocardial infarction in Sweden. The coverage is high and in 2019, 92% of all patients in Sweden up to 80 years of age with myocardial infarction were entered in the registry. At the investigating hospital, the coverage is 98%, and data entry is continuously monitored both internally and externally.

3.1.4 Study populations

In study I, all patients for whom a pre-hospital ECG was transmitted to the investigating hospital during 2013 were eligible for inclusion. Patients with faulty transmissions, or transmissions intended for other hospital sites (3%) were excluded.

In study II, all patients with STEMI at the investigating hospital between 17 December 2010 and 27 July 2015 were eligible for inclusion. Patients who did not arrive by ambulance, or in case a pre-hospital ECG had not been transmitted, or if coronary angiography was either not performed or if it was delayed for more than six hours, were excluded.

3.1.5 Other main variables

Information on background demographics and clinical presentation was obtained from medical charts (Take Care®, CompuGroup Medical, Sweden). The status of whether a pre-hospital CL activation had been performed or not was recorded from locally stored information on all pre-hospital ECGs, and confirmed in the medical charts.

3.2 STUDY III

3.2.1 Study population

All adult patients, admitted for AMI at two participating hospitals, were eligible for inclusion if the clinical echocardiogram early after the AMI revealed an LVEF ≤ 40%. Exclusion criteria were limited to short life expectancy (within one year), vast comorbidity or refusal to participate in the study. Both participating hospitals, Danderyd Hospital and Sodersjukhuset, are large teaching hospitals in the urban Stockholm area.

3.2.2 Echocardiographic examinations

Patients were invited to undergo baseline resting echocardiography and a low-dose dobutamine stress echocardiography within one week after the AMI, before discharge from the hospital. Repeated echocardiography was performed after three months. Standard commercially available equipment was used for the recording and storing of the examinations as well as for the post-processing analyses; GE Vivid 7 and GE EchoPac (GE Vingmed, Norway).

For the resting examinations, a standard echocardiographic examination was conducted. For the low-dose dobutamine stress echocardiography, 2D and tissue Doppler images were acquired from the apical 4-chamber, 2-chamber and 3-chamber views. A continuous infusion of dobutamine at 5 μg/kg/min was then administered through an intravenous line for three minutes, after which time the dose was increased to 10 μg/kg/min. After another three minutes, the apical images during low-dose dobutamine infusion were obtained. A contrast enhancing agent for left ventricular opacification, SonoVue (Braccho, Italy) was used if more than 20% of the endocardial border was poorly visualized.

LVEF was measured using the Simpson Biplane method. Two members of the research team independently reviewed and measured the LVEF. If there was less than a five percentage point difference between the observers, an average was recorded. If the difference was greater than five percentage points, a third member of the team was consulted and a consensus was reached. Inter and intra observer analyses were performed.

Mitral annular plane systolic excursion (MAPSE) and peak systolic velocity (PSV) were measured from the apical tissue Doppler images (figure 5). For MAPSE, an average of the 4-chamber and 2-chamber views was used. For PSV, the average was based on all six basal segments from the three standard apical views. The use of MAPSE using tissue Doppler, instead of the conventional M-mode analysis, was beneficial as for most points the same region of interest could reveal information on both MAPSE and PSV. MAPSE measured by M-mode vs. tissue Doppler has been shown to have close correlation, R = 0.86 (109).

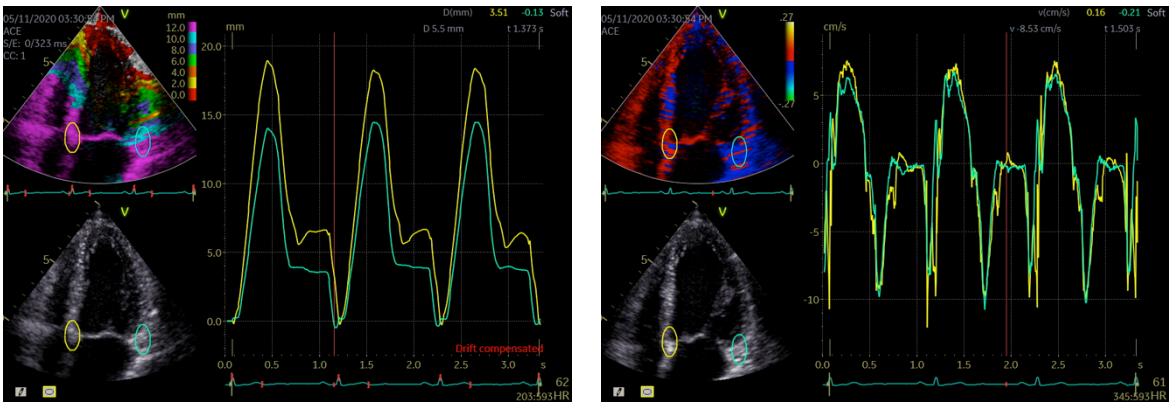


Figure 5: In the tissue Doppler images, a region of interest was placed in each of the segments surrounding the mitral annulus. Mitral annular plane systolic excursion (MAPSE, left panel) and peak systolic velocity (PSV, right panel) were measured. Printed by courtesy of Elif Günyeli.

3.2.3 Main outcome and other variables

The main outcome variable was LVEF ≤ 35% at the three-month follow-up visit. Information on background demographics and clinical status was collected during study inclusion and at the three-month visit.

3.3 STUDY IV

3.3.1 Study population

The study population in study IV was the same as that of study III, with the exception that all nine patients from Sodersjukhuset were excluded. The rationale for excluding those patients was that the discharge ECG was not always obtainable through the electronic medical chart system, and also due to the small number of patients.

3.3.2 ECG analysis

Discharge ECGs were obtained through clinical practice, but such ECGs were not always available. If no discharge ECG was found in the medical charts, the ECG closest to one week after the AMI was used. ECGs were analyzed for rhythm, heart rate, PQ-interval, QRS-interval, the presence of bundle branch blocks or hemiblocks, ventricular pacing, persistent ST-segment elevations, and pathologic Q-waves or R-wave progression. For the three last mentioned variables, the definitions stated in table 3 were used, and these findings were only studied in patients who did not have intra-ventricular conduction abnormalities (bundle branch blocks, hemiblocks or ventricular pacing).

3.3.3 Main outcome and other variables

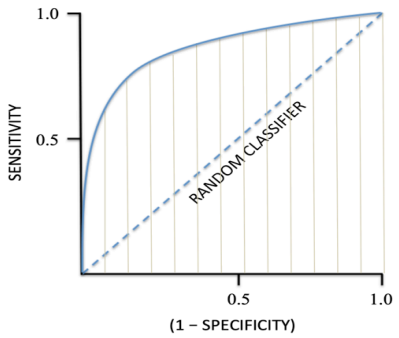
The main outcome in study IV was the dichotomous variable of ICD status. For the secondary outcome, medical charts were reviewed to see if the participant had died during the long-term follow up. If so, the date and cause of death was recorded from the death certificate or through review of the medical chart. Information on whether a life-threatening arrhythmia had occurred was also obtained from the medical charts.

3.4 STATISTICS

Continuous variables were analyzed for normal distribution by visual inspection of the histograms and by the Shapiro Wilk's test. Normally distributed continuous variables were described by mean and standard deviation and were compared by the independent or dependent t test where appropriate. Categorical variables were presented as numbers and percentages and compared using the chi-squared test, unless the number in any cell was less than six in which case Fisher's exact test was used.

In study I, quantile regression was used to compare medians of the time intervals, and in study II the Wilcoxon Rank-Sum test was used. Quantile regression was also used in study II for the multiple variable regression analysis of the time from first medical contact to ECG. Quantile regression is a regression tool that does not require the assumptions necessary in linear regression models. It allows for comparison of any quantile of interest, and also allows for adjusting for other covariates (110).

In study III, receiver operating characteristics curves (ROC) were graphed and the area under the curves (AUC)s were analyzed and compared using the DeLong method (111). The ROC AUC is equivalent to the C-statistic. Cut-off values were set to reach the maximal area under the curve, and the sensitivity, specificity, positive and negative predictive values were presented (figure 6).



		Gold standard	
		Has the disorder	Does not have the disorder
Test	Test is positive	a	b
	Test is negative	c	d

Figure 6: An example of a receiver operating characteristics (ROC) curve where the sensitivity is plotted on the Y-axis and (1 – specificity) on the X-axis. A continuous variable with a 50-50 chance of predicting an outcome would render a line such as the dotted blue line. The area under the curve (AUC) is illustrated by the brown lines. The sensitivity (a/(a+c)), specificity (d/(b+d)), positive predictive value (a/(a+b)) and negative predictive value (d/(c+d)) can then be established.

In study IV, the cumulative probabilities of the outcomes were graphed using Kaplan Meier curves and differences between groups were compared using the Log-Rank test. Hazard ratios were provided by the use of univariable and multivariable Cox regression analyses.

For all statistical analyses a two-tailed p value ≤ 0.05 was considered significant. All analyses were performed using Stata/SE 14.2 (Statacorp LLC, USA).

3.5 ETHICAL CONSIDERATIONS

All studies were in accordance with the Declaration of Helsinki (112). For studies I and II, permission was requested from the regional ethics committee, that ascertained that the studies did not require formal permission (DNR 2014/294-31). For studies III and IV, permission was granted (DNR 2010/882-31/2) and (DNR 2020-04690) and formal written consent was obtained from each study participant.

For all studies, the medical charts of study participants were reviewed which could compromise personal integrity. In order to protect the integrity of study participants, several precautions were taken. All members of the study team were medical personnel accustomed to reviewing confidential information and to the laws of patient confidentiality. All data that was collected on paper was stored in a locked room in the research unit, as was the study key uniting study identification numbers to personal identification numbers. All digital information was stored on secure servers and no personal identification numbers were recorded in the digital databases. All results were presented on group level without the possibility of identifying individual study participants.

For studies I and II, no further interventions, examinations or follow-up visits were done other than those included in standard medical care.

For study III, echocardiographic examinations, including a low-dose dobutamine stress echocardiogram, were performed and follow-up visits requested. Echocardiographic examinations are conducted with the patient lying down and a probe pressed against the subject's chest. This may cause a slight discomfort for patients, especially in the early post-AMI setting. Patients may also experience a slight discomfort upon administration of dobutamine, which may cause palpitations, hypotension and a sensation of stress. In study III, the dobutamine infusion was administered at a low concentration with a slow and gradual increase, and this is generally well tolerated by patients. Also, the stress part of the test was quick, usually less than ten minutes. During the examination an intravenous line had to be present, which can be slightly painful and comes with a small risk of infections or thrombophlebitis. All patients in study III however, were already admitted to the hospital for AMI and already had an intravenous line inserted. The additional risk of complications regarding this was therefore considered very low.

For both studies III and IV, the three month follow-up visit might be seen as a burden to the study participants, having to travel back to the hospital for study visits. This should also be seen in perspective as all the study participants had an at least moderately reduced LVEF and had experienced an AMI. These patients would have been invited to follow-up visits regardless of inclusion in the study. Study participation did therefore not add extra visits beyond what was already implemented in clinical practice.

For the long-term follow-up in study IV, no further visits were necessary and all of the long-term follow-up was done by medical chart review.

4 RESULTS

4.1 BASELINE CHARACTERISTICS

Background demographic information on the study populations in studies I – IV is summarized in table 9. All studies involved patients with AMI or for whom STEMI was highly suspected. In general, patients were around 70 years old and 65 - 77% of them were male. Around 20% had diabetes and almost 50% had a previous diagnosis of hypertension. Background characteristics were rather similar in all four studies, with the exception for smoking status, which was numerically higher in study I and likely due to the fact that previous smoking was included in the smoking definition used in that study.

Table 9: Baseline characteristics of the study populations in studies I – IV. All values presented as numbers (percentages) if not otherwise specified.

	Study I	**Study II**	**Study III**	**Study IV**
Patients	Patients with pre-hospital CL activations (n = 115)	STEMI patients with pre-hospital ECGs (n = 539)	Patients admitted for AMI with LVEF ≤ 40% (n = 96)	Patients admitted for AMI with LVEF ≤ 40% (n = 87)
Age, years, median [IQR]	68 [60 - 75]	67 [59 - 76]	71 [62 - 77]	71 [62 - 78]
Gender, male	75 (65)	385 (71)	73 (76)	66 (77)
Smoking	63 (55)	136 (25)	29 (30)	26 (30)
Diabetes Mellitus	21 (18)	104 (19)	19 (20)	18 (21)
Hypertension	54 (47)	263 (49)	46 (48)	42 (48)
Prior myocardial infarction	13 (11)	87 (16)	13 (14)	13 (15)
Prior PCI	10 (9)	66 (12)	11 (12) [1]	10 (11) [1]
Prior CABG	3 (3)	-	-	-
Previous heart failure	-	-	15 (16)	15 (17)
Atrial fibrillation	-	-	13 (14)	13 (15)

[1] Patients with previous revascularization, either PCI or CABG

AMI = Acute Myocardial Infarction, CABG = Coronary Artery Bypass Graft, CL = Catheterization Laboratory, IQR = Inter Quartile Range, LVEF = Left Ventricular Ejection Fraction, PCI = Percutaneous Coronary Intervention, STEMI = ST-segment Elevation Myocardial Infarction

4.2 STUDY I

4.2.1 Accuracy in STEMI diagnosis

During the study period, and after exclusion of test ECGs or incorrectly transmitted pre-hospital ECGs, 4,298 patients were included in the study. A flow chart of the study patients, pre-hospital CL activations and final diagnosis of STEMI is found in figure 7. Among the included patients, there were 115 (3%) pre-hospital CL activations based on pre-hospital information regarding symptoms and ECG. Background characteristics are found in table 9. STEMI-diagnosis was confirmed in 97 (84%) of these patients, yielding a rate of false-positive CL activations of 16% (95% CI 10 – 23%).

Among the remaining 4,183 patients, STEMI was found in 42 (1%) patients. One third of these patients had been directly admitted to the coronary care unit (CCU), indicating a high index of suspicion and also allowing for quick assessment and, if necessary, quick access to the CL. However, 28 patients were directed to the emergency department (ED). Among them, nine patients had ST-segment elevations on the pre-hospital ECG (six with inferior location, two with anterior location and one with lateral location).

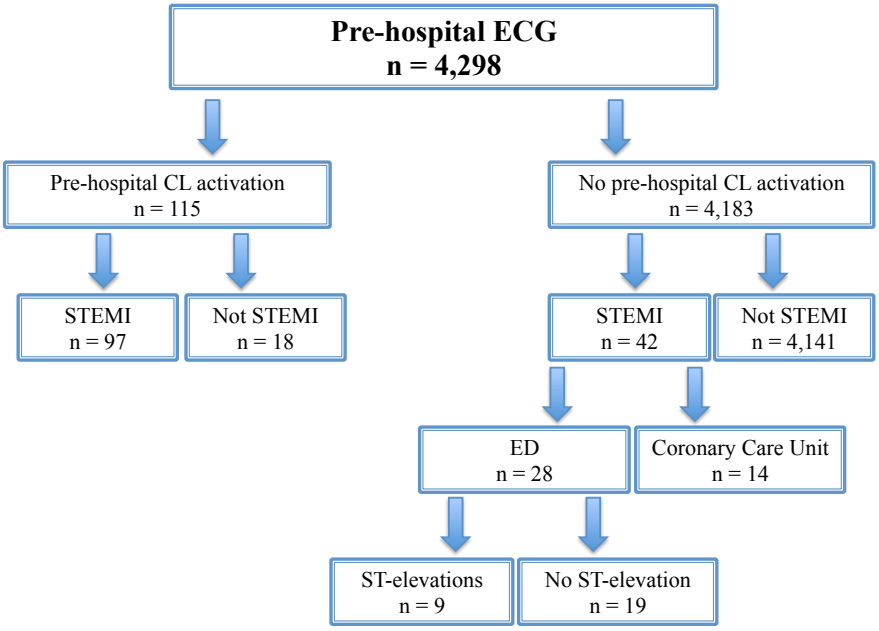


Figure 7: Flow chart of study the cohort in study I, including information on pre-hospital CL activations and final diagnosis of STEMI. CL = Catheterization Laboratory, ED = Emergency Department, STEMI = ST-segment Elevation Myocardial Infarction

4.2.2 Delay time analyses

For the 115 patients with pre-hospital ECGs, a detailed analysis of the various delay time intervals was performed (figure 8). The median time from emergency call to arterial puncture was 76 minutes [IQR 65 - 90] and from ambulance arrival to arterial puncture 45 minutes [IQR 35 - 54]. There were no significant differences between true STEMI patients and

patients with other diagnoses. For patients presenting during office hours, defined as non-holiday weekdays between 8 a.m. and 4 p.m., the time between arrival at the hospital and arterial puncture was significantly shorter, median 16 vs. 26 minutes ($p = 0.001$). This led to a significantly longer delay time between emergency call and arterial puncture for patients arriving during on-call hours; 80 vs. 67 minutes, $p = 0.003$.

There was a difference in time from the arrival of the ambulance to the transmission of pre-hospital ECG between women and men. The median time for women was 20 minutes vs. 13 minutes for men ($p < 0.001$). Despite this, there was no significant difference in total time from emergency call to arterial puncture between men and women.

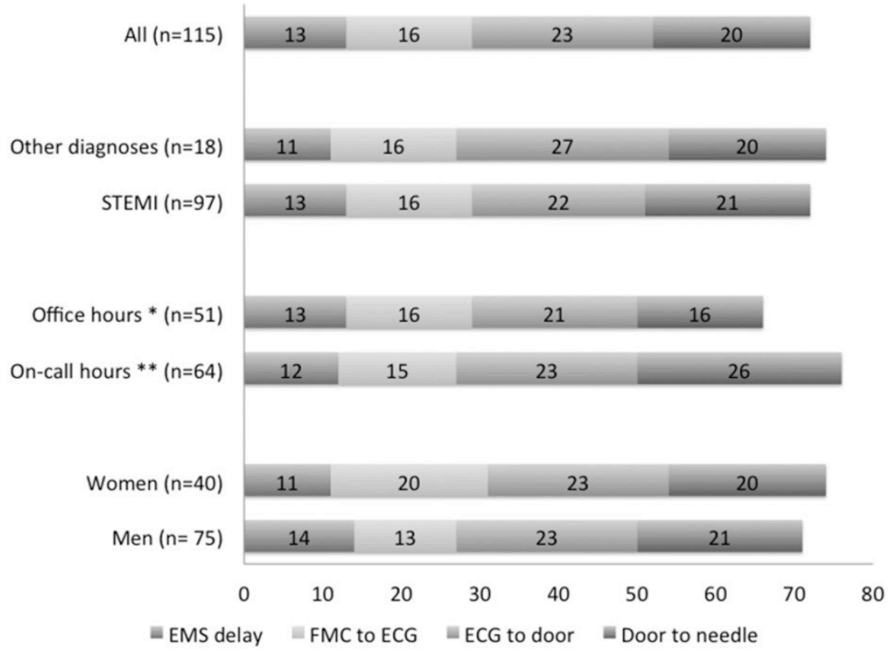


Figure 8: Delay time intervals for 115 patients with a pre-hospital catheterization laboratory activation. EMS = Emergency Medical Services, FMC = First Medical Contact (time that ambulance arrived at patient location), Office hours = Non-holiday weekdays 8 a.m. – 4 p.m., On-call hours = all other times, STEMI = ST-segment elevation myocardial infarction. Scandinavian Cardiovascular Journal, 52:2, 74-79. Reprinted with permission from Taylor & Francis Group.

The time target of acquiring a pre-hospital ECG within ten minutes of ambulance arrival was met for 16%. Arrival of the ambulance to arterial puncture within 60 minutes was reached for 83%, and within 90 minutes for 98% of the patients.

4.3 STUDY II

4.3.1 Patient selection

During the study period, 916 STEMI cases were identified at the investigating hospital through the SWEDEHEART registry. After exclusion of STEMI-patients who did not arrive by ambulance, or for whom a pre-hospital ECG was not transmitted, or who either did not undergo coronary angiography or if the angiography was delayed more than six hours after arrival at the hospital, 539 patients remained. A flow chart describing the patient selection is found in figure 9. Background characteristics are found in table 9.

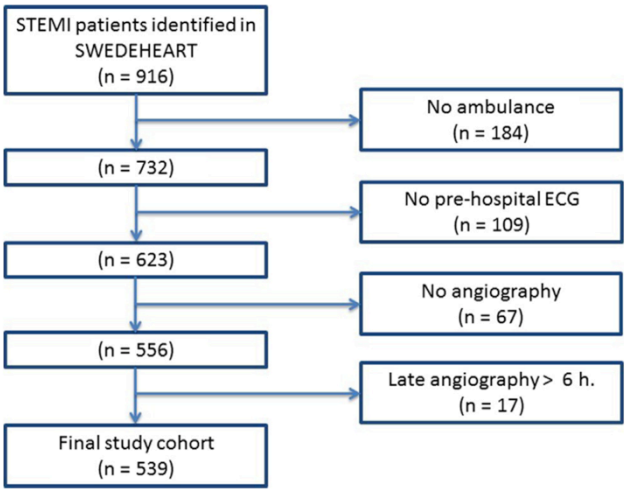


Figure 9: Flow chart describing patient selection in study II. ECG = Electrocardiogram, STEMI = ST-segment Elevation Myocardial Infarction. SWEDEHEART = Swedish Web-system for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies. International Journal of Cardiology 26 (2020), 100458. Reprinted by permission from Elsevier.

4.3.2 Pre-hospital ECG within ten minutes and delay time analyses

The target of obtaining a pre-hospital ECG within ten minutes of ambulance arrival was met for 22% of the cohort; 29% of the men vs. 14% of the women ($p = 0.001$). Time from emergency call to arterial puncture within 90 minutes was reached for 81% of the men and 82% of the women ($p = 0.557$), and time from pre-hospital ECG to arterial puncture within 90 minutes was achieved for 88% of the men and 89% of the women ($p = 0.697$).

Time from symptom onset to emergency call was significantly longer for women, 61 vs. 45 minutes ($p = 0.031$). Also, the median time from ambulance arrival to ECG was three minutes longer for women than for men (median 17 vs. 14 minutes, $p < 0.001$) (figure 10). After adjusting for age, smoking, LVEF and hypertension, a time difference of two minutes remained ($p = 0.018$). There were no other significant differences in the other delay time intervals, or in the total time from emergency call to arterial puncture, between men and women.

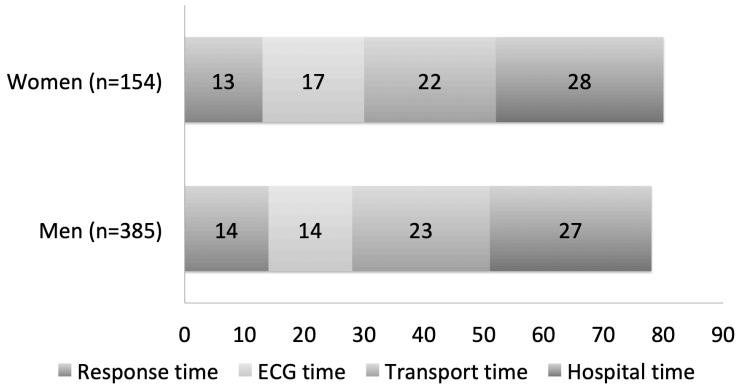


Figure 10: Delay time intervals for 539 patients with STEMI, arriving by ambulance and for whom a pre-hospital ECG had been transmitted. Data from study II, International Journal of Cardiology 26 (2020), 100458.

4.4 STUDY III

4.4.1 Study population

In study III, 96 patients admitted for AMI at either of the two participating hospitals, and who had an LVEF ≤ 40% were included. Baseline characteristics are found in table 9. There were 80 patients who underwent both the low-dose dobutamine stress echocardiography and the three-month follow-up resting echocardiography.

4.4.2 Echocardiographic parameters

Resting and low-dose dobutamine stress echocardiographic examinations were performed 4 [IQR 3-6] days after the acute myocardial infarction. Median time to repeat echocardiogram at three months was 92 days [IQR 90 – 98].

Patients who met the primary outcome of LVEF ≤ 35% three months after the myocardial infarction had significantly lower LVEF, MAPSE and PSV both during resting echocardiography and low-dose dobutamine stress echocardiography (table 10). A contractile reserve, defined as an absolute increase in LVEF of ≥ 5 percentage units (113), was found during low-dose dobutamine stress echo for 50% of the patients without LVEF recovery and 77% of the patients with LVEF > 35% at three months (p = 0.012).

Table 10: LVEF, MAPSE and PSV during resting and low-dose dobutamine echocardiography, by groups of patients meeting the ICD-criteria of LVEF ≤ 35% at three months or not. All data presented as mean ± standard deviation if not otherwise specified. Data from study III (Open Heart 2019;6:e001053).

	LVEF ≤ 35% at three months (n = 32)	**LVEF > 35% at three months (n = 48)**	**p**
LVEF rest, %, median [IQR]	28 [24 – 32]	35 [33 – 39]	< 0.001
LVEF low-dose dobutamine, %	33 ± 10	44 ± 10	< 0.001
MAPSE rest, mm	6 ± 1	8 ± 2	0.003
MAPSE low-dose dobutamine, mm	7 ± 1	9 ± 2	0.005
PSV rest, cm/s	3.4 ± 0.8	4.1 ± 1.0	0.002
PSV low-dose dobutamine, cm/s	4.6 ± 1.1	5.4 ± 1.8	0.042

ICD = Implantable Cardioverter Defibrillator, IQR = Interquartile Range, LVEF = Left Ventricular Ejection Fraction, MAPSE = Mitral Annular Plane Systolic Excursion, PSV = Peak Systolic Velocity

4.4.3 The diagnostic ability of resting and low-dose dobutamine stress echocardiography before discharge

The echocardiographic parameters LVEF, MAPSE and PSV, during resting and low-dose dobutamine stress echocardiography before discharge from the hospital, were graphed against the outcome LVEF > 35% at three months in ROC curves (figure 11). The greatest AUC was found for resting LVEF, with an AUC of 85% (95% CI 74 – 94). None of the other variables yielded a higher AUC, including after stratifying for atrial fibrillation, myocardial infarction prior to the index infarction in the study, CABG or STEMI/non-STEMI.

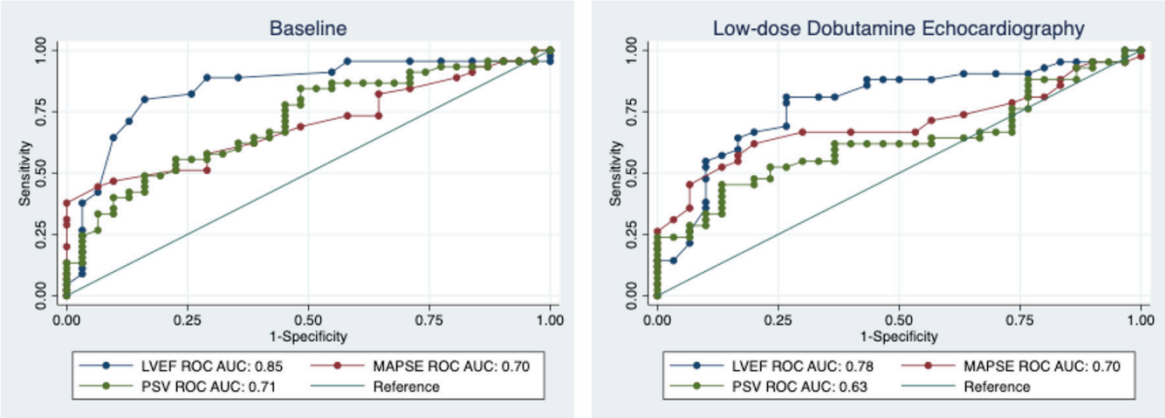


Figure 11: Receiver Operating Characteristic curves on the discriminatory ability of resting and low-dose dobutamine stress echocardiography in determining LVEF > 35% at three months. AUC = Area Under the Curve, LVEF = Left Ventricular Ejection Fraction, MAPSE = Mitral Annular Plane Systolic Excursion, ROC = Receiver Operating Characteristics. Open Heart 2019;6:e001053. Reprinted by permission from BMJ Publishing Group Ltd.

4.4.4 Performance of binary classifications

The ROC curves were inspected and cut-off values selected. Sensitivity, specificity, positive and negative predictive values were calculated and summarized in table 11. All studied variables resulted in fairly high sensitivities around 90-95%, but at the same time fairly low specificities around 50%.

Table 11: Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of different echocardiographic measurements in the detection of LVEF ≤ 35% at three months. Data from study III (Open Heart 2019;6:e001053).

	Cut-off	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
LVEF rest	≤ 35%	94	40	51	90
LVEF low-dose dobutamine	≤ 45%	91	56	58	90
MAPSE rest	≤ 8 mm	94	44	54	91
MAPSE low-dose dobutamine	≤ 9 mm	93	45	55	90
PSV rest	≤ 5 cm/s	97	13	43	86
PSV low-dose dobutamine	≤ 6 cm/s	90	31	48	81

LVEF = Left Ventricular Ejection Fraction, MAPSE = Mitral Annular Plane Systolic Excursion, PSV = Peak Systolic Velocity

4.5 STUDY IV

4.5.1 Study population and ICD implantation

There were 87 patients included in study IV, who were followed on average for 6.1 ± 2.1 years. Background characteristics are found in table 9. During the follow-up time, 26 (30%) patients received an ICD. The median time from AMI to ICD was 127 [IQR 21 – 170] days.

There were no statistically significant ECG differences in terms of rhythm, ventricular frequency, PQ-interval, QRS-interval, or the presence of intra-ventricular conduction abnormalities between those who received an ICD and those who did not (table 12). Patients who did not receive an ICD were, however, more often female (70% vs. 92%, p = 0.027), and were more likely to have diabetes (29% vs. 4 %, p = 0.010) and had less often a myocardial infarction prior to the index infarction in the study (10% vs. 27%, p = 0.041).

Table 12: General ECG findings in study cohort and differences between patients who received an ICD vs. those who did not. All values presented as numbers (percentages) if not otherwise specified.

	All (n = 87)	Received ICD (n = 26)	No ICD (n = 61)	p
Sinus rhythm	78 (90)	25 (96)	53 (87)	0.269
Atrial fibrillation	7 (8)	0	7 (11)	0.098
Ventricular frequency, beats/min, median [IQR]	76 [67 - 90]	72 [61 - 79]	79 [71 - 90]	0.054
PQ interval, ms, median [IQR]	170 [150 - 190]	170 [150 - 190]	170 [150 - 190]	0.925
QRS interval, ms, median [IQR]	90 [90, 110]	95 [90, 130]	90 [85, 100]	0.191
Intra-ventricular conduction abnormalities (LBBB, RBBB, pacemaker, LAH, LPH)	19 (22)	8 (31)	11 (18)	0.188

ICD = Implantable Cardioverter Defibrillator, IQR = Interquartile Range, LAH = Left Anterior Hemiblock, LBBB = Left Bundle Branch Block, LPH = Left Posterior Hemiblock, ms = milliseconds, RBBB = Right Bundle Branch Block.

4.5.2 Prediction of need for an ICD by ECG

Apart from the 19 patients with intra-ventricular conduction abnormalities, the discharge ECGs for the remaining 68 patients were examined for the presence of pathologic Q-waves, pathologic R-wave progression and remaining ST-segment elevations. Patients who received an ICD more often had a pathologic R-wave progression than those who did not (83% vs. 46%, p = 0.011). Pathologic R-wave progressions and also lateral Q-waves were both predictors of an increased risk for ICD implantation in the univariable analysis (table 13). After adjusting for gender, previous myocardial infarction and the diagnosis of STEMI, the increased risk remained. For those with a pathologic R-wave progression, the adjusted HR was 4.0 (95% CI 1.1 – 14.3, p = 0.033) for the identification of ICD patients. This risk remained when LVEF was also included in the model (HR 4.0, 95% CI 1.2 – 14.9, p = 0.035).

The sensitivity for either pathologic R-wave progression or pathologic Q-waves for the detection of ICD patients was 83%. In the total cohort, there were fifteen (17%) patients who did not have pathologic Q-waves, pathologic R-wave progression or intra-ventricular conduction abnormalities. None of them received an ICD during follow-up, and none of them suffered from malignant arrhythmias during the study period. Four of the patients died during the follow-up period, but none due to SCD.

Table 13: Cox regression analysis for ICD-implantation, n = 68. Multivariable analysis adjusted for gender, previous myocardial infarction prior to the index infarction, and STEMI diagnosis.

	Univariable		Multivariable	
	HR (95% CI)	p	HR (95% CI)	p
Presence of pathologic Q-waves	2.70 (0.78-9.33)	0.117	2.03 (0.52-7.89)	0.307
Anterior location	0.88 (0.34-2.26)	0.783	0.79 (0.29-2.16)	0.645
Lateral location	5.54 (1.56-19.65)	0.008	4.79 (1.28-17.87)	0.020
Inferior location	1.61 (0.57-4.53)	0.365	1.14 (0.40-3.21)	0.809
Pathologic R-wave progression	4.98 (1.44-17.26)	0.011	4.00 (1.12-14.32)	0.033
Remaining ST-elevation	2.43 (0.91-6.50)	0.076	2.37 (0.79-7.13)	0.125

4.5.3 Cumulative ICD or CRT-D treatment

Survival curves of cumulative ICD or CRT-D treatment were graphed using Kaplan-Meier curves (figure 12). Patients with pathologic R-wave progression were significantly more likely to receive an ICD than patients who did not (Log Rank p = 0.005). Combining the ECG parameters, none of the patients who did not have intra-ventricular conduction abnormalities, pathologic Q-waves or a pathologic R-wave progression received an ICD during the follow-up period (figure 12D).

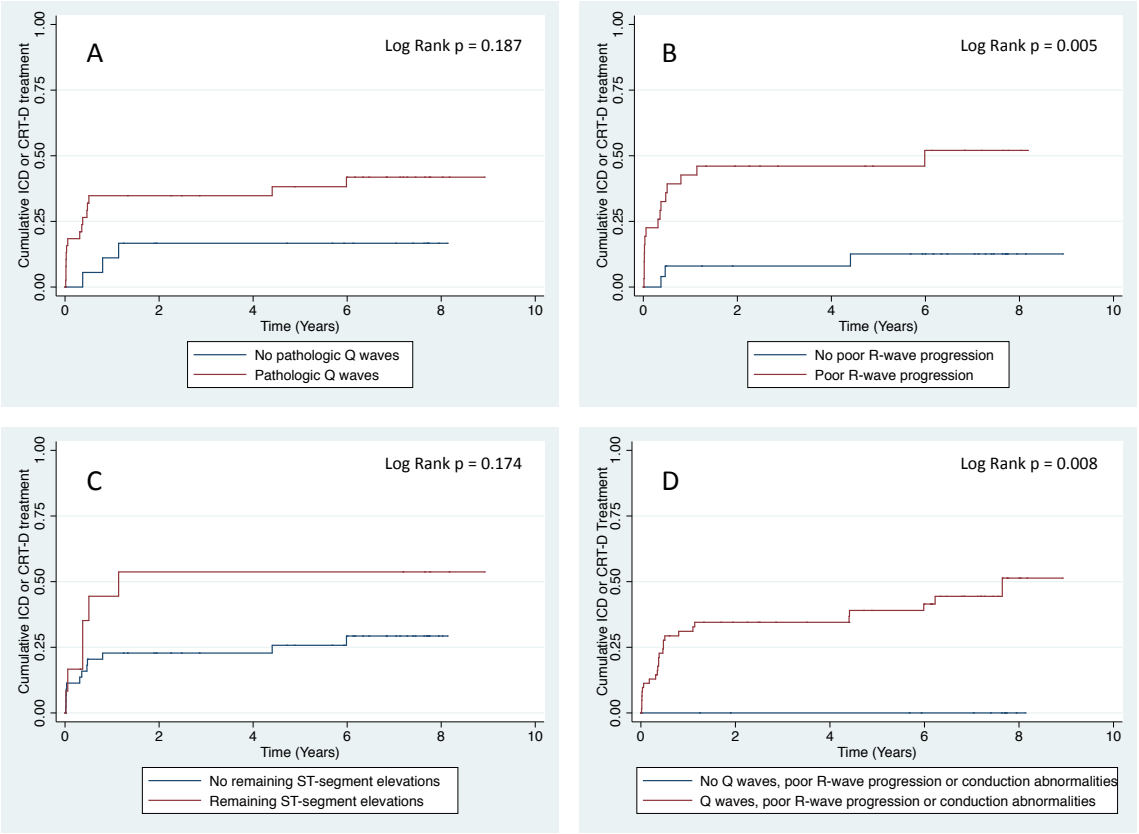


Figure 12: Kaplan-Meier graphs on cumulative ICD or CRT-D treatment. Graphs A-C include the 68 patients included in the ECG analysis, while graph D includes the full cohort of 87 patients. Patients grouped by: A) pathologic Q waves, B) pathologic R-wave progression, C) remaining ST-segment elevations and D) either pathologic Q waves, pathologic R-wave progression or intra-ventricular conduction abnormalities.

CRT-D = Cardiac Resynchronization Therapy – Defibrillator, ICD = Implantable Cardioverter Defibrillator.

5 DISCUSSION

5.1 MAJOR FINDINGS

In study I, one in six patients with a suspected STEMI based on pre-hospital ECGs was discharged with an alternative diagnosis. Measured from the time of arrival of the ambulance, the time target of reperfusion therapy within 90 minutes was achieved for almost all patients (98%), but the achievement of a pre-hospital ECG within ten minutes was only met for 16% of the cohort. The delay time to pre-hospital ECG was significantly longer for women than for men.

In study II, a pre-hospital ECG was obtained within ten minutes for only around one fifth of the patients, and the target was more likely to be achieved for men than for women. Almost 90% reached the target of reperfusion therapy within 90 minutes. Women had a significantly longer delay time between symptom onset and emergency call.

In study III, among patients with an at least moderately reduced LVEF after an AMI, 60% recovered their LVEF to ≥ 35% after three months. Patients with LVEF ≤35% at three months had a significantly lower left ventricular function at both resting and stress echocardiography measured by LVEF, MAPSE and PSV before discharge. Baseline LVEF was a good predictor of recovery with a ROC AUC of 85%, and none of the other variables, including those measured during stress echocardiography, were better discriminators.

In study IV, patients with LVEF ≤ 40% after an AMI and who had a pathologic R-wave progression on the discharge ECG were four times more likely to receive an ICD compared to those with normal R-wave progressions. None of the patients without a pathologic R-wave progression, pathologic Q-waves, or intra-ventricular conduction abnormalities, received an ICD or suffered from malignant arrhythmias during the follow-up period.

5.2 STEMI DIAGNOSIS

5.2.1 Why study the rate of false-positive STEMI diagnoses?

The benefit of rapid management of STEMI patients is well supported and has been discussed in chapters 1.6 and 1.7. Every 30-minute delay is associated with a relative risk of around 1.08 for one-year mortality (114). Also, every hour of delay is an independent predictor for heart failure with a HR of 1.10 (95% CI 1.02 – 1.17) (115). But are there problems associated with being too fast?

In a hypothetical scenario, if the availability of catheterization laboratories and staff were unlimited all patients included in study I (n = 4,298) could have been referred directly to coronary angiography. Although only 139 of these patients were true STEMI patients, for them fifteen minutes could have been saved by not acquiring a pre-hospital ECG. Further, it can be speculated that with unlimited access to the catheterization laboratory, another fifteen minutes could be saved due to improvement of in-hospital systems, such as having the teams ready and working at all hours. In this scenario, it is possible that 30 minutes of ischemic time

could be saved. Assuming that the one-year mortality rate at the investigating hospital in study I is similar to the one reported by De Luca et al. (5.8%) (114), the hypothetical situation would reduce the annual number of deaths from 8.1 patients to 7.4 patients. Also, using data from Desta et al. that 28% of the STEMI patients develop heart failure (91) and extrapolating data that there is a 10% increase in the risk of heart failure for every additional hour of delay (115), this would mean that number of heart failure patients would be reduced from 39 to 37. On the other hand, there would be 4,298 – 139 = 4,159 coronary angiograms performed for patients unlikely to benefit from them. Although the risk of complications during angiographic examinations has decreased vastly over the years, based on published rates of complication the experiment of referring all patients with pre-hospital ECGs to the CL would cause 103 cases of contrast induced nephropathy, 42 pseudo-aneurysms and 33 deaths (complication rates based on those reported by Tavakol et al.) (116). Assuming a cost of around 10,000 SEK for each angiogram (personal communication, Dr. Persson, Danderyd Hospital), this scenario would also put a ≈ 43 million SEK (≈ 5.1 million USD) financial burden on the hospital budget for this single center alone. Also, there would be a need for a vast increase in the number of catheterization laboratories, staff, and other resources. It is clear that careful patient selection is motivated.

5.2.2 What is a correct STEMI diagnosis?

In order to find the true rate of false-positive STEMI diagnoses, a clear definition of a correct diagnosis is needed. The definition of a correct STEMI diagnosis is somewhat complicated. At the time of diagnosis in the pre-hospital setting, biomarkers are usually not available and the diagnosis is based on the evaluation of the clinical scenario and the pre-hospital ECG. In many systems, the person initiating the pre-hospital CL activation is not on location in the ambulance, but will have to rely on the reports of the clinical status by telephone communication with EMS staff. This may affect decision-making, and the rates of false-positive CL activations may differ depending on whether the patient was evaluated in person in the emergency department or by indirect communication. Also, the ECG can be equivocal and true ST-segment elevations are not always present in the setting of an occluded coronary vessel. Several other ECG configurations have been identified as “STEMI-equivalents” (figure 13).

Even the definition of an occluded coronary is by itself not enough for the diagnosis of STEMI. Among the 12,657 patients with STEMI-diagnosis included in the FITT-STEMI trial (Feedback Intervention and Treatment Times in ST-elevation Myocardial Infarction), 0.3% of the patients had no “coronary arteries narrowed” (117) and in a meta-analysis combining eight independent randomized STEMI trials (n = 14,929), 0.2% of the patients were excluded due to the fact that they had non-significant obstructions in the infarct related artery (118). In both these examples, the percentage of patients without occluded or critically compromised coronary arteries was very low. This is likely due to the fact that other diagnoses were offered to patients without coronary lesions, thus excluding them from participation in the studies.

When looking at a more unselected material, such as in clinical practice, the lack of finding a culprit vessel on coronary angiography is significantly higher as was seen in table 4.

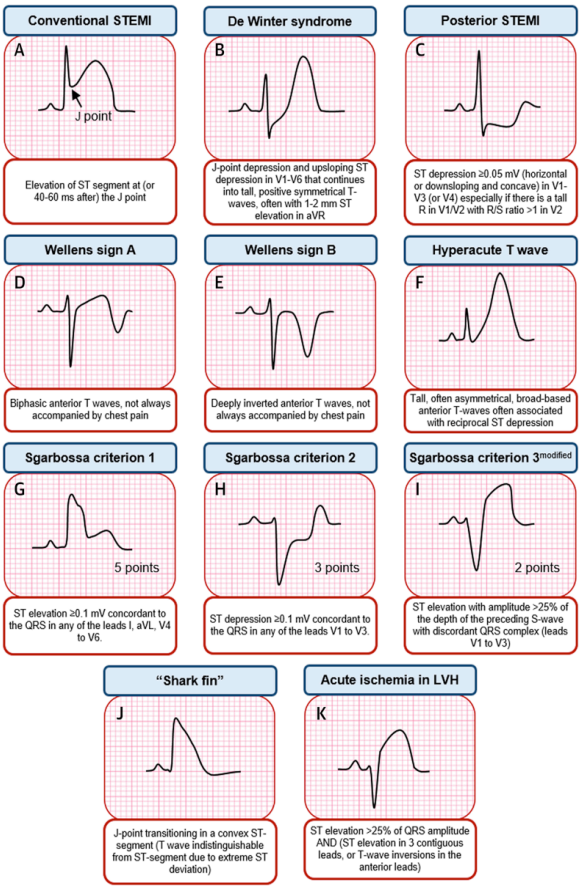


Figure 13: ECG patterns associated with a high risk of critical coronary artery stenosis or occlusions. Asatryan el al, Electrocardiographic Diagnosis of Life-Threatening STEMI Equivalents – When every minute counts. JACC:Case Reports.2019;1(4):666-8. Reprinted by the permission of the CC BY-NC-ND LICENSE http://creativecommons.org/licenses/by-nc-nd/4.0.

Further more, a significant proportion of patients diagnosed with non-STEMI have occluded arteries. In one meta-analysis including 40,777 patients, 25.5 % were found to have an occluded coronary artery (119).

In studies I and II, the definition of a true STEMI was based entirely on what was entered in the national quality registry SWEDEHEART. Based on the fourth universal definition of myocardial infarctions, in order to establish that a type 1 acute myocardial infarction is present, there is a need for both elevated cTn levels and one of either symptoms, ECG findings, imaging evidence or identification of a coronary thrombus by angiography (14). Only symptoms, possibly information regarding risk factors, and a pre-hospital ECG are available in the field setting, thus making a final diagnosis of STEMI impossible at such an early stage. The results of the investigations performed later, during hospital admission, such as coronary angiography, lab results including cTn, echocardiography and the clinical

scenario will certainly contribute to whether a final diagnosis of STEMI is set or not. This was the motivation of using the SWEDEHEART entry as the main outcome variable in study I, and inclusion variable in study II.

5.2.3 The rate of false-positive STEMI

The rate of false-positive pre-hospital CL activations was 16% for the detection of patients with STEMI in study I. The patients who had pre-hospital CL activations but did not receive a STEMI diagnosis were diagnosed with unspecific chest pain, non-STEMI, pericarditis, angina pectoris, dilated cardiomyopathy, left bundle branch block, cardiac arrest, or pancreatitis. The patient who suffered from cardiac arrest could not be resuscitated. No autopsy was performed and it is possible that this patient could have been misclassified as not having STEMI. For that patient, and the patient with pancreatitis, no angiography was performed. It can easily be argued that all of the remaining patients with pre-hospital CL activations the angiographies were still beneficial for identifying or ruling out significant coronary lesions. Then, if using the somewhat subjective outcome "necessary emergency coronary angiography", the rate of false-positivity in study I would be reduced from 16% to 1% (that percent being the patient with pancreatitis).

Taken into consideration all the discussed difficulties in establishing what a true STEMI diagnosis really is, especially in the pre-hospital setting, and also the complex nature of human biology, the rate of false-positives is unlikely to ever be zero. An analogy can be drawn to what surgeons have experienced in appendectomies. Traditionally, surgeons have accepted a false-positive rate in performing appendectomies for appendicitis of approximately 20%, in order to reduce morbidity that can follow missed diagnoses (120). However, between 1996 and 2006, reports from one hospital found a decrease from 24% to 3% ($p < 0.001$) due to advances in pre-operative imaging (ultrasound and computerized tomography) (121). Can something similar be done in pre-hospital STEMI care? The use of portable troponin assays that can be used in the out-of-hospital setting has shown promising results. Stopyra et al. found that obtaining a point of care troponin level in the pre-hospital setting was feasible for 83% of the attempts (122). The authors report a sensitivity of 27% and a specificity of 92%. In a Danish cohort, Sorensen et al. report that a pre-hospital troponin level was feasible to obtain in 97% of the attempts and that the values could identify 30% of patients diagnosed with AMI (123). The use of pre-hospital cTn in a broader clinical perspective remains to be seen.

The rate of false-positive pre-hospital STEMI diagnoses will thus depend highly on the definition of population studied, in what time aspect, and how the diagnosis STEMI is defined. Nevertheless, the importance of having some type of follow-up regarding this has been stressed. In a Swedish setting, the combination of the different registries in SWEDEHEART could easily provide continuous monitoring and benchmarking regarding this, possibly with a slight modification in the input variables. Based on the findings in study I, and the studies presented in table 4, a proposed target of around 15% seems plausible.

5.3 TIME COMPONENTS AND GENDER DIFFERENCES

5.3.1 Patient delay

In study II there was a difference in median time from symptom onset to emergency call between men and women, where women called emergency services about fifteen minutes later than men. Larger reports from SWEDEHEART and ISACS-TC, have found differences of around 30 minutes (76, 77), and in the Vienna registry, a difference was 19 minutes was found (124). It is possible that the slightly lower time difference between the genders reported in study II is due to the smaller number of patients or regional differences in behavior in when to seek medical care. The clinical significance of patient delay is important and it is likely that time to presentation contributes to the increased mortality among women seen in many studies. In the Vienna registry for example, the increased mortality both during hospital stay and during long-term follow-up seen in the univariable regression model, was no longer significant when adjusted for clinical covariates and time to presentation (124). Although not being the sole factor for prognosis, it is unlikely that a longer delay from symptom onset to medical attention would be beneficial in any way.

A possible cause for the longer patient delay times for women could be due to variations in clinical presentation. In a Swedish questionnaire-based study among 532 STEMI admitted to the CCU, chest pain was less common among women than among men (74% vs. 93%, $p < 0.001$), whereas other symptoms such as nausea (49% vs. 29%, $p < 0.001$) and shoulder pain (33% vs. 15%, $p < 0.001$) were more frequent (125).

In studies I and II, the remaining delay time intervals are all less than 30 minutes. The symptom delay times reported from Vienna were 109 vs. 91 minutes (124), in SWEDEHEART 210 vs. 180 minutes (76), in ISACS-TC 270 vs. 240 minutes (77) and in study II 61 vs. 45 minutes for women vs. men. Viewing this in relation to the fact that the rest of the delay time between emergency call to arterial puncture was around 80 minutes in study II, it is likely that in order to improve the chain of care for patients with STEMI even further, efforts should be made to make patients with STEMI seek emergency care sooner.

5.3.2 Delay in diagnosis

In both studies I and II, only a low proportion of patients with possible STEMI is diagnosed by pre-hospital ECG within ten minutes from EMS arrival. In study I the proportion was 16% and in study II 22%. The ESC has issued a class IB recommendation of a target delay of no more than ten minutes to obtain an ECG (15). This recommendation is based on two references (126, 127). The first study is based on data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Pectoris Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) Quality Improvement Initiative study, and included data from over 63,000 patients with non-STEMI seeking care in the emergency department. In that study, reported by Diercks et al., 35% had an initial ECG taken within ten minutes from arrival at the hospital. After adjusting for clinical factors (including age, gender and comorbidities) and

hospital factors (including teaching vs. non-teaching facilities and physician specialty) no differences were found neither in death nor post-admission myocardial infarction (126). The second study motivating the class IB classification is a pooled analysis of ten independent registries in the United States, reported by Rokos et al. The study included 2,712 patients who were diagnosed with STEMI by the use of pre-hospital ECGs. Among the 2,053 patients who underwent primary PCI, the authors found a door-to-balloon time ≤ 90 minutes for 86% and an ECG-to-balloon time ≤ 90 minutes for 68% of the patients (127). The measurement of time from ambulance arrival to pre-hospital ECG was not the aim of the article although it is briefly mentioned in the discussion.

While the impact of the use of pre-hospital ECGs in STEMI care is well supported, it thus seems as the impact of the acquisition of such an ECG within ten minutes is much less supported. A small report by Studnek et al. among 165 STEMI patients with a pre-hospital STEMI alert, the median time from EMS arrival to pre-hospital ECG was 5.1 minutes. Adjusting for age, gender and race, the authors report that patients with pre-hospital ECG within eight minutes were more likely to reach time to reperfusion ≤ 90 minutes, OR 3.4 (95% CI 1.2-9.3) (128).

Whatever the optimal time from ambulance arrival to pre-hospital ECG is, it is likely that every minute counts even in this phase of the total ischemic time. STEMI care monitoring system or registries, that focus mainly on monitoring times from the STEMI diagnosis (including pre-hospital ECG based) might thus miss an important part of the delay time. If the acquisition of a pre-hospital ECG is much delayed, e.g. in the ambulance five minutes prior to arrival in the hospital, the time from STEMI-diagnosis to reperfusion will be short. If the pre-hospital ECG is taken in the patient's home, prior to loading the patient in the ambulance, the performance of the hospital will look "worse" if the time is measured from the time of the ECG. It is likely that the measurement of the whole time chain, from the onset of symptoms to reperfusion therapy, as well as the discussed time intervals in between, will provide a less biased view of the total ischemic time.

5.4 WHO NEEDS AN ICD AFTER A MYOCARDIAL INFARCTION?

5.4.1 The optimal outcome in studies aiming to predict future ICD candidates

The aim of studies III and IV was to identify predictors, before discharge from the hospital and while the patient was still admitted for an AMI, for the eligibility of ICD therapy according to guideline recommendations. In study III the best echocardiographic predictor of finding patients with LVEF ≤ 35% after three months was resting LVEF with a ROC AUC of 85%. In study IV patients with a pathologic R-wave progression had a four-fold increased risk of obtaining an ICD during the study period. There are strengths and limitations in the choice of outcomes used in these studies. In the MADIT II and SCD-HeFT studies, both demonstrating reductions in mortality by ICD treatment in post-AMI patients, the inclusion criteria included LVEF ≤ 30% (MADIT II) and LVEF ≤ 35% (SCD-HeFT) (104, 105). Later,

it became clear in the DINAMIT and IRIS studies, that LVEF measured early after an AMI is not a sufficient criterion to select patients for ICD treatment (107, 108). Nevertheless, despite all the limitations that exist regarding LVEF, this parameter has consistently been shown across studies to be a strong and robust prognostic marker. In both the DINAMIT and IRIS trials, the risk of arrhythmia related death was reduced by the early implantation of ICDs, but the risk of non-cardiac deaths was increased.

An ICD is unlikely to prevent any other types of deaths than those that are arrhythmia related, and hence the identification of malignant arrhythmias would probably be the best outcome. Studies III and IV were not designed to use SCD or malignant arrhythmias as primary outcome and the number of patients in the studies that experienced such arrhythmias was relatively low (9% in study III, 14% in study IV). In one study, based on the patients with heart failure after AMI who were included in the VALIANT study but who died, autopsy reports were available for 398 patients. Among them, 26% were classified as have died due to SCD, and among them 51% were presumed to be due to arrhythmic causes and 42% due to fatal myocardial infarctions (remaining causes of SCD were heart failure, overdose, pulmonary embolism or stroke) (129). It is however likely that at least a proportion of the patients who died due to recurrent myocardial infarctions also had malignant arrhythmias. In a hypothetical calculation, if 100 patients with heart failure die after an AMI, and 26% of them are SCD, and say 60% of those with SCD are arrhythmia related, then sixteen patients could possibly be saved by an ICD. The absolute risk reduction would hence be around 16% and the number needed to treat 6.4.

The use of risk scores has been suggested and examples include the Duke Sudden Cardiac Death Risk Score (130) and the risk score proposed by Docherty et al. (131). The ROC AUC of the Duke Score was 0.75 (internal validation) and 0.64 (external validation), and for the Docherty score 0.72. Both these scores include LVEF as well as other clinical characteristics, but their usefulness in clinical practice for the identification of ICD candidates after an AMI remains to be seen.

In study IV, the main outcome used in the study was ICD implantation. The decision of placing a primary preventive ICD is generally not done until after re-evaluation of LVEF 6-12 weeks after the AMI. Current guidelines recommend that ICDs be offered to patients with symptomatic heart failure with LVEF ≤35% measured after at least six weeks after the AMI despite optimal medical therapy, and who are expected to live for at least one year with good functional status (15). The decision of treatment with an ICD does not come without bias. One retrospective study previously published by the study group found inadequate follow-up in 32% of the patients, mostly due to the fact that no follow-up echocardiography was ordered (132). Similar findings have been reported from another study group in Israel where 29% did not have repeat echocardiography (133). This highlights the need for identification of ICD candidates before hospital discharge. In the study setting in studies III and IV, this was perhaps less likely to happen due to the fact that the patient was enrolled in a study, but it may affect generalizability as follow-up in clinical practice is usually not as rigorous as in a

research study. Nevertheless, even in the study setting 17% of enrolled patients who underwent the first low-dose dobutamine stress echocardiographic examination did not do the three month examination, mostly due to vast comorbidity.

5.4.2 The role of stress echocardiography

In study III, none of the studied stress echocardiography measurements were superior to baseline LVEF in the prediction of patients meeting the ICD criteria of LVEF ≤ 35% after three months. Still, baseline LVEF, was a strong discriminator with a ROC AUC of 85% (numerically higher than the risk scores mentioned in chapter 5.4.1). As mentioned in the introduction, stress echocardiography is known to be able to identify myocardial viability and contractile reserve. In hibernating segments of the myocardium with severely reduced perfusion the response to dobutamine can be either absent or below visual detection. This may lead to a number of false-negatives. The sensitivity of the dobutamine stress echocardiography to detect viability with functional recovery is around 75-80% (134). Resting LVEF after myocardial infarction has been shown to be a predictor of recovery at three months to LVEF ≥ 35%, and patients with resting LVEF 31-35% are almost seven times more likely to recover than patients with LVEF ≤ 25% (135).

In study III, only LVEF, MAPSE and PSV were analyzed during baseline and low-dose dobutamine stress echocardiography. It is possible that these measurements are too global in a sense that more regional abnormalities are not accounted for. In a study by Swinburn et al., a Wall Motion Score during low-dose dobutamine stress echocardiography provided incremental information over resting data in terms of predicting death and non-fatal AMI (136). This was not measured in study III as the aim was to find less time-consuming methods that were easier to obtain in clinical practice. More advanced parameters such as strain or strain rate, have been shown to be predictors of both total infarct size and death after an acute myocardial infarction (137). This is true for both patients with reduced LVEF and normal LVEF post-infarction (138, 139). However, measurement of global strain by speckle tracking is dependent on good image quality, which is not always feasible in the clinical setting. This was also the reason for usage of more easily quantifiable parameters such as MAPSE and PSV in study III.

5.4.3 The role of discharge ECG

In study IV, the main finding was that patients with a pathologic R-wave progression after an AMI had a four-fold increased risk of treatment with an ICD during the follow-up period. Patients without a pathologic R-wave progression, pathologic Q-waves, or intra-ventricular conduction abnormalities were identified as a low-risk group and in study IV no such patients received an ICD.

For patients with AMI, normal ECGs have been associated with an improved prognosis. In one observational study (n = 391,208), patients with AMI and with a normal initial ECG had an approximately 40% lower risk of in-hospital mortality, compared to those patients with ST-segment elevations, ST-segment depressions or LBBB (140). Viewing discharge ECGs

for AMI patients, both remaining ST-segment depressions and remaining Q-waves have been associated with both an increased risk of re-infarction and death within six months (141). However, having an increased risk for all-cause mortality is not synonymous to having a possible benefit from ICD implantation. For example, although QRS duration has been associated with increased mortality (142) it did not predict ventricular arrhythmias in patients with ICDs (143).

In study IV, although there was a trend towards statistical significance, patients with pathologic Q-waves did not have an increased risk of ICD implantation. A possible explanation could simply be due to lack of power, although the number of cases in the R-wave calculation was similar to the number in the Q-wave calculation. Another possible explanation could be that the current definition of pathologic Q-waves was not robust enough. The classic definition of Q-waves (duration ≥ 40 ms and/or depth ≥25% of R) has been shown to be better correlated with infarct size measured by cardiac magnetic resonance than the newer classification of Q-waves used in study IV (44).

5.5 LIMITATIONS

Studies I and II were single center observational studies which may affect generalizability. The investigating hospital is one of the largest cardiology clinics in Sweden with a high number of various types of cardiology patients, including STEMI patients, each year. According to SWEDEHEART data, the performance of the investigating hospital in STEMI care is high. Also, due to its location in an urban setting, the times of transportation are likely to be shorter than in more rural parts of Sweden and the world. Despite the vast experience of the hospital, the rate false-positive pre-hospital STEMI diagnosis of about 16%. It is possible that this rate is higher in sites with less experience, and the importance is perhaps not the number itself but fact that it should be monitored.

The fact that the time target of the acquisition of a pre-hospital ECG within ten minutes was only met for around 20% of the study cohort, even for patients with STEMI, is concerning. A majority of patients for whom a pre-hospital ECG is obtained do not have STEMI. These patients are likely to have more unclear symptoms, and it is possible that the time to pre-hospital ECG is even longer for that group. In study II, only patients with true STEMI were included in the study, and we can therefore not make inference on ambulance performance in an unselected material.

The time of ambulance arrival, both at the patient location and at the hospital, was logged by ambulance staff and later obtained by ambulance charts. The logging of correct times could possibly be affected by patient status, e.g. if the patient was unstable the log time could have been delayed. It was not possible to retrospectively check if the correct time was entered by EMS and it is not possible to rule out some degree of non-random misclassification. However, as all patients in the main analysis in study I had pre-hospital CL activations, and all patients in study II had STEMI, it is likely that such misclassifications would rather provide longer delay times than the “truth”, and if anything might under-estimate the

proportion of patients receiving reperfusion within 60 or 90 minutes. Time of ambulance call and pre-hospital ECG was recorded by automatic clock and those times are therefore more robust.

The definition of STEMI used studies I and II was based on the entry in the national quality registry SWEDEHEART. This was discussed in chapter 5.2.2. The coverage of SWEDEHEART is highest for patients under the age of 80 and might not be complete for older patients. In study I, medical charts for all patients in the main analysis were scrutinized and there were no additional STEMI patients found. Also, the investigating hospital has a high coverage especially for patients with STEMI, regardless of age. The fact that cases would unintentionally be excluded is unlikely.

Most of the patients in study III, and all of the patients included in study IV, were also included from a single center. Patients in all four studies had relatively similar baseline characteristics. However, invasive and medical treatment for patients with AMI in sites with less experience or lower patient volumes may be different. For instance, after an AMI at the investigating hospital, close follow-up with dedicated nurses and outpatient treatment follows. According to the study protocol, patients in studies III and IV were all invited for a repeat echocardiography three months after the myocardial infarction. Although 17% did not do the three-month echocardiogram, the percentage of failure to repeat echocardiography is higher in clinical settings.

LVEF was the main predictor variable and also the main outcome variable in study III. Although seemingly an easily obtained echocardiographic measurement the measurement of LVEF can be subjective and incorrectly quantified. In order to reduce this, each LVEF measurement was done by at least two independent members of the study team and intra and inter observer correlations were reported. Also, measurements of MAPSE and PSV, which generally show less variability, were reported. It is likely that the use of contrast enhancing agents or the use of 3D echocardiography for all patients would have improved LVEF precision.

6 CONCLUSIONS

The rate of false-positive catheterization laboratory activations, based on pre-hospital ECGs and information, is low and similar to rates reported by studies on in-hospital diagnoses. Also, the goal of achieving reperfusion within 90 minutes is obtained for most patients. Female patients have longer delay times from symptom onset to emergency call. Also, for all patients but especially for female patients, the goal of obtaining a pre-hospital ECG within ten minutes is reached for only a fraction of patients with true or possible STEMI.

For patients who are diagnosed with AMI and who have a reduced LVEF during admission, a majority of patients will recover the LVEF to $\geq 35\%$ at three months. Although lower LVEF at baseline predicted non-recovery, measurement of LVEF, MAPSE and PSV on low-dose dobutamine stress echocardiography did not add further information. However, patients with pathologic R-wave progression before discharge from the hospital were four times more likely to receive an ICD during follow up. Patients who did not have pathologic R-wave progression, or Q-waves or intra-ventricular conduction abnormalities were unlikely to receive an ICD or malignant arrhythmias and could be considered to be a low-risk group.

7 CLINICAL IMPLICATIONS

In order to reduce morbidity and mortality for patients with STEMI, management of such patients needs to be fast and correct. The importance of studying time intervals can give important clues on where the time bandits are and can thus provide information on where efforts of improvement should be focused. In study I, the rate of false-positive pre-hospital STEMI alerts was relatively low. However, this was a single center study and even if the same definition of true STEMI is used, it is likely that the number will vary both over time and also between different sites. Using the quality registry SWEDEHEART and information from SCAAR (the Swedish Coronary Angiography and Angioplasty Registry, a part of SWEDEHEART), the rate of false-positive pre-hospital catheterization laboratories could easily be monitored for all sites treating patients with STEMI in Sweden. Benchmarking and comparisons between sites could be done and time trends assessed. Also, by obtaining large data regarding the rate of false-positives, it is likely that the optimal target regarding this could be established and possibly the care for patients with STEMI improved.

Studies I and II both address the fact that among patients with suspected or true STEMI, a pre-hospital ECG within ten minutes from ambulance arrival is obtained for only around 20%. The time target of ten minutes, established by international guidelines, does not have a strong evidence-based background and despite the fact that most patients did not have a pre-hospital ECG within ten minutes, the over-all time target of reperfusion therapy within 90 minutes was met for almost all patients. Time intervals could also efficiently be monitored by the use of SWEDEHEART. Only measuring time from ECG to reperfusion therapy can easily lead to false conclusions. Easily obtainable time measurements, such as time of emergency call, time of ambulance arrival, time of pre-hospital ECG, time of arterial puncture and time of wire passage are all parts of the ischemic time that is affected by EMS and hospital performance, and should be monitored. The fact that women seem to wait longer after symptom onset could possibly be addressed by information campaigns, but should then also be monitored continuously in order to see if the efforts are effective.

Study III revealed that the measurement of LVEF, MAPSE and PSV on low-dose dobutamine stress echocardiography did not add further information on which patients improve their LVEF to more than 35% after three months. It is possible that more advanced echocardiographic measurements on low-dose dobutamine stress echocardiography could be used to discriminate better, but study III does not support the use of routine stress-echocardiography after an AMI.

For patients with a reduced LVEF after an AMI, the discharge ECG contains prognostic information and should be obtained for all patients. Patients with either a pathologic R-wave progression, pathologic Q-waves or intra-ventricular conduction abnormalities have a higher risk of needing an ICD in the future than patients who do not. More comprehensive studies will have to demonstrate if early implantation of an ICD is beneficial for this group or not.

8 FUTURE PERSPECTIVES

In all four studies in this thesis the sample sizes were relatively small and the studies were in general limited to one investigation site. It is possible that, in the future, most of the findings from all four studies in fact could be obtained from the national quality registry SWEDEHEART. For studies I and II, only small adjustments to the input variables in the sub-registries Riks-HIA and SCAAR need to be made in order for continuous monitoring of false-positive rates, time intervals and gender differences. Most sites in Sweden report very short delay times, usually measured as time from the ECG that confirmed ST-segment elevations to arterial puncture. This time interval will miss all the false-negative pre-hospital ECG interpretations as the pre-hospital ECG is then, in some scenarios, never even taken into consideration when measuring hospital performance. A proposed way of addressing this would be to enter time of emergency call, time of pre-hospital ECG and information on whether such an ECG was used to activate a pre-hospital STEMI alert. This would be a better way to monitor the performance of the pre-hospital part of the time chain.

The search of patients suitable for early implantation of ICDs continues. Studies addressing this face the challenge that the rate of sudden cardiac death or resuscitation from malignant ventricular arrhythmias is relatively low and large studies with long follow-up need to be conducted. Big data from national registries could facilitate patient inclusion, but are not always as detailed studies III and IV. For example detailed discharge ECG information is lacking. Merging of the level I national cardiac arrest registry and SWEDEHEART and analyzing obtainable background information and in-hospital information, could possibly identify a risk score to identify patients with the highest risk of SCD, similar to the CHA_2DS_2 VASc risk score for the risk of thromboembolism in patients with atrial fibrillation. After internal and external validation, further studies would then have to demonstrate the benefit of early ICD implantation, and what cut-off values are optimal.

9 SVENSK SAMMANFATTNING

Introduktion

Trots stora framsteg inom hjärtinfarktvården är hjärtinfarkt en av de vanligaste dödsorsakerna i världen. För patienter med hjärtinfarkt och ST-höjningar på EKG (STEMI) har snabb handläggning visat sig vara associerad med en bättre prognos både avseende död och följdsjukdomar såsom hjärtsvikt. Flera åtgärder inom den prehospitala vårdkedjan kan påskynda handläggningen för dessa patienter. Exempelvis kan patienter, med hjälp av trådlös överföring av prehospitala EKG från ambulans till sjukhus, hänvisas direkt till kranskärlsröntgen. Värdefull tid kan då sparas. Det är dock viktigt att ha en korrekt diagnos tidigt, eftersom patienten hänvisas direkt till en utredning med invasiva metoder utan att remitterande läkare har haft möjlighet att direkt träffa patienten. Att ställa en korrekt diagnos under dessa förutsättningar kan vara utmanande för den remitterande läkaren. Internationella riktlinjer har satt upp mål för hur lång tid olika aspekter inom vårdkedjan för STEMI-patienter högst bör ta. Könsskillnader i måluppfyllelse avseende dessa tidsaspekter, samt måluppfyllelsen att ta ett prehospitalt EKG inom tio minuter från ambulansens ankomst är inte noga studerade.

För patienter som överlever en hjärtinfarkt kvarstår en risk för bestående eller övergående hjärtsvikt. Graden av hjärtsvikt kan kvantifieras med hjälp av ekokardiografi. Det är visat att patienter med en försämrad hjärtfunktion, definierat som låg ejektionsfraktion, har en försämrad prognos jämfört patienter med normal ejektionsfraktion. För de patienter som har en kvarstående låg ejektionsfraktion trots optimal medicinsk behandling tre månader efter en hjärtinfarkt, kan en implanterbar defibrillator (ICD) förbättra överlevnaden. Vinsten med ICD-behandling ses dock inte förrän efter flera månader efter en hjärtinfarkt. Detta kompliceras av det faktum att risken för plötslig hjärtdöd är som högst under den första tiden efter en hjärtinfarkt. Därför skulle det vara fördelaktigt att finna prediktorer för de patienter som kan bli föremål för ICD-behandling tidigt efter en hjärtinfarkt, allra helst under vårdtiden.

Mål

Det övergripande målet med avhandlingen var att finna enkla och kliniskt relevanta mått på EKG och ekokardiografi som kan förbättra prognosen för patienter med akut hjärtinfarkt. Mer specifikt var huvudmålen:

Studie I: Att studera andelen falskt-positiva STEMI-patienter där diagnosen har ställts baserat på prehospital information.

Studie II: Att studera könsskillnader avseende tidsintervaller i handläggningstid för STEMI-patienter och att studera hur ofta målet att erhålla ett prehospitalt EKG inom tio minuter från ambulansens ankomst nås.

Studie III: Att studera om stressekokardiografi med lågdos dobutamin kan särskilja de patienter som återhämtar sin vänsterkammarfunktion efter en hjärtinfarkt, från de patienter som inte gör det.

Studie IV: Att undersöka om utskrivnings-EKG i samband med ett vårdtillfälle för hjärtinfarkt kan användas för att predicera vilka patienter som kan komma i åtanke för ICD-behandling.

Metod

I studier I och II utgjorde alla konsekutiva patienter, för vilka ett prehospitalt EKG hade sänts till det undersökande sjukhuset, studiebasen. I studie I var insamlingstiden januari – december 2013 och i studie II december 2010 till juli 2015. I studie I erhölls information om huruvida ett prehospitalt STEMI-larm hade utfärdats via medicinska journaler. För båda studier inhämtades information om STEMI-diagnos från kvalitetsregistret SWEDEHEART. Tidsintervaller beräknades med hjälp av tidsangivelser från patientjournal, ambulansjournal, databas för prehospitala EKG och SWEDEHEART.

I studier III och IV inkluderades vuxna patienter som vårdades inneliggande för hjärtinfarkt och hade en ejektionsfraktion högst 40 %. Kort förväntad överlevnad och ovilja att delta i studien utgjorde exklusionskriterier. I studie III utfördes en stressekokardiografisk undersökning med lågdos dobutamin under vårdtiden för hjärtinfarkten. I studie IV studerades det EKG som togs innan patienten skrevs ut från sjukhuset.

Resultat

I studie I var det 115 patienter som remitterades direkt från ambulans till kranskärlsröntgen för misstänkt STEMI. Av dessa var det 16 % (95 % CI 10-23%) som skrevs ut med annan diagnos än STEMI. Tidsmålet för reperfusionsbehandling inom 90 minuter uppnåddes för nästan alla patienter (98 %), men målet med prehospitalt EKG inom tio minuter från ambulansens ankomst nåddes endast för 16 % av kohorten. Tiden till prehospitalt EKG var signifikant längre för kvinnor än för män; median 20 minuter jämfört med 13 minuter ($p < 0.001$).

I studie II inkluderades 539 patienter med STEMI för vilka ett prehospitalt EKG hade sänts till det undersökande sjukhuset. För 22 % av kohorten hade det prehospitala EKGt tagits inom tio minuter. Målet nåddes i högre grad för män än för kvinnor (29 % jämfört med 14 %, $p = 0.001$). Trots detta, nåddes målet med reperfusionsbehandling inom 90 minuter för 88 %

av alla patienter och det förelåg ingen könsskillnad avseende detta. Kvinnor hade dock en signifikant längre tid mellan symtomdebut och larmsamtal än män.

I studie III inkluderades 96 patienter med ejektionsfraktion ≤ 40 % som vårdades inneliggande för hjärtinfarkt. Av dem genomgick 80 patienter både stressekokardiografi med lågdos dobutamin under vårdtiden samt ett uppföljande tremånaders eko. Av dessa 80 patienter, var det 32 (40 %) patienter som hade en ejektionsfraktion ≤ 35 % efter tre månader. Dessa patienter hade signifikant lägre värden avseende ejektionsfraktion och longitudinell funktion i samband med hjärtinfarkten. Ejektionsfraktion i vila hade en ROC AUC på 85 % (95 % CI 74-94%) för detektion av förbättring. Inga av de andra studerade parametrarna, varken på vilo-ekokardiografi eller stressekokardiografi med lågdos dobutamin, hade större ROC AUC.

I studie IV studerades utskrivnings-EKG på 87 patienter som ingick i studie III. De som hade en nedsatt R-vågsprogression hade en fyra gånger ökad risk att erhålla en ICD under uppföljningstiden. Ingen av patienterna som inte hade en nedsatt R-vågsprogression, eller patologisk Q-våg, eller intraventrikulära ledningshinder erhöll en ICD under uppföljningstiden, och ingen av dem drabbades av livshotande arytmier.

Sammanfattning

Bland de patienter som remitteras direkt från ambulansen till kranskärlsröntgen för misstänkt STEMI, är andelen patienter som skrivs ut med alternativa diagnoser låg och väl jämförbar med rapporter baserade på akutmottagningens bedömning. Tidsmässigt finns könsskillnader där män generellt har en kortare tid mellan symtomdebut och larmsamtal samt mellan ambulansankomst och prehospitalt EKG. Målet att ta ett prehospitalt EKG inom tio minuter nås endast för ungefär en femtedel av patienterna och det finns stort utrymme till förbättring avseende detta.

För patienter med hjärtsvikt efter en hjärtinfarkt är ejektionsfraktion en stark prediktor för framtida förbättring. Enkla mått med stressekokardiografi med lågdos dobutamin tillförde ingen prognostisk information. Patienter med en nedsatt R-vågsprogression i samband med en hjärtinfarkt har en signifikant ökad risk att behöva en ICD, medan patienter som varken har en nedsatt R-vågsprogression, patologiska Q-vågor eller intraventrikulärt ledningshinder kan ses som en lågrisk population.

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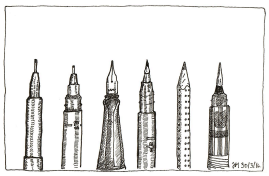
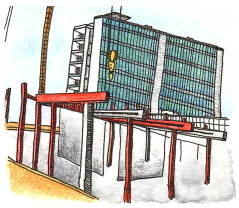
A list of further acknowledgements is found in table 14.

Table 14: Sample of main contributors to this thesis (n = 45). Please enjoy the small symbolic gifts. Names will appear only once, although the person might belong to several categories. Names are presented in alphabetical order by surname within each category.

Category	Names	Contribution	Gift
Mentor	Jaran Eriksen	We worked our first day together at the department of Clinical Pharmacology and we were roommates during my rotation there. Thank you for being my mentor and making me feel that you were always just one phone call away.	
Co-authors	Eva Andersson, Lars Eurenius, Eli Maliniak, Jonas Persson	Thank you all for you valuable input in turning our research ideas into published articles. Jonas, extra thanks for your input regarding coronary angiography	
Heads of department	Karin Malmqvist, Raffaele Scorza	Thank you for all your support and setting an atmosphere at the clinic where research work is both valued and encouraged.	
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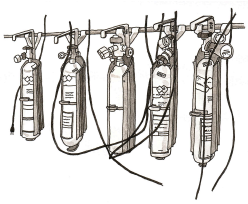
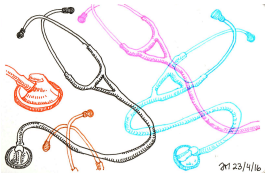
Karolinska Institutet Research School	Gabriella Bröms, Eva Piscator, Eva Willis	When I was asked to give feedback on the Karolinska Institutet Research School in Epidemiology, the only negative thing that I could think of was that it ended. Thank you for organizing and conducting it so well. Eva P, thank you for all the early study mornings in your conference room.	
Echo colleagues	Fozia Abbas, Maria Carbajal, Elif Günyeli, Marie Kilström, Lars-Göran Nordin, Kambiz Shahgaldi, Reidar Winter	Thank you for encouraging me to learn the art of echocardiography and helping me taking the first few steps toward the unachievable goal of reaching echo nirvana. Thank you all for making going to work feel like going to meet your friends. Home away from home.	

Table 14: continued.

Category	Names	Contribution	Gift
Cardiology Clinic	Inge Björkander, Katrín Guðmundsdóttir, Kristina Hagwall, Patrik Hjalmarsson, Ann Samnegård, Emma Svennberg	Thank you all for being an important part of my journey. Patrik and Inge, I would probably not have become a cardiologist if it were not for your persistent support. Emma and Katrín, thank you for all our research discussions and also the EMS and JOM journal club series. Kristina, you know you are my idol and Ann, you know you are my role model. Thank you.	
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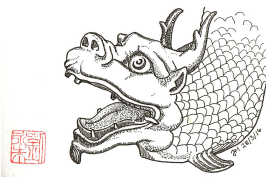
Friends	Anders Löfving, Sofia Ottemo, Mats Rundgren, Siw Rundgren, Mirta Stupin	Without your support and close friendship over the years, I would not have made it this far. Thank you for all the fun moments we have had and those that are yet to come. Sofia, thank you also for helping me with the cover graphics. Mats, thank you for proof reading.	
Family	Julia Muhrbeck, Paul Muhrbeck, Anna Yu, Christina Yu, Peter Yu, Tae-Jong Yu	Thank you for your support and that you always value education and hard work. I would also extend my gratitude to my family overseas and to the Muhrbeck family.	
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