MARKKU ESKOLA

Use of the 12-lead Electrocardiogram in Selecting Reperfusion Therapy for ST-elevation Myocardial Infarction

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ACADEMIC DISSERTATION
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University of Tampere, Medical School
Tampere University Hospital, Heart Center
Finland

Supervised by
Docent Kari Niemelä
University of Tampere
Finland

Reviewed by
Docent Markku Mäkijärvi
University of Helsinki
Finland
Docent Jouko Remes
University of Turku
Finland

Distribution
Bookshop TAJU
P.O. Box 617
33014 University of Tampere
Finland

Tel. +358 3 3551 6055
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ABSTRACT

Immediate reperfusion, by fibrinolytic therapy (FT) or primary percutaneous coronary intervention (PCI), is the preferred treatment for acute ST-elevation myocardial infarction (STEMI). Rapid identification, risk stratification and choice of reperfusion strategy are initially based on 12-lead electrocardiogram (ECG) findings. It is important to identify, by noninvasive methods, high-risk subgroups who need transfer to a 24h/7d invasive treatment centre. Computerized ECG algorithms, often used in out-of-hospital settings, have a potential to enhance early ECG interpretation, but their performance must be validated against manual algorithms. Acute anterior myocardial infarction (MI) caused by proximal occlusion of the left anterior descending coronary artery (LAD), is associated with unfavourable outcome and should be recognized by simple non-invasive methods such as ECG. Using two distinct ECG patterns it is possible to predict the stage of the infarct process in the myocardium. The pre-infarction syndrome (PIS) is defined as ST elevation accompanied by positive T waves without pathological Q waves, while evolving myocardial infarction (EMI) is reflected in the ECG by pathological Q waves and/or negative T wave.

The aims of the present study were to evaluate the comparative accuracy of lead-specific computer-based vs. manual measurements of J-point, ST-segment and T-wave deviations in 12-lead ECGs (**I**); to develop a computer-assisted model to detect proximal occlusion of the LAD in patients with suspected acute coronary syndrome (ACS) (**II**); to study the clinical outcome of ECG and angiographic signs of proximal vs. distal LAD occlusion (**III**); and to assess the prognostic value of the PIS and EMI ECG patterns with respect to reperfusion strategy (**IV**).

The original study population for studies **I** and **II** comprised 531 consecutive patients admitted to the emergency room and evaluated for suspected MI. For studies **III** and **IV** the patients (n=1522) with STEMI were randomly assigned to FT or primary PCI.

Bland-Altman analysis demonstrated clinically acceptable limits of agreement in comparing measurements of the J point and the T wave, but clinically inadequate limits of agreement with respect to ST-segment deviation, between manual and computer analysis. Computer-analysed ST-elevation values were constantly smaller than manually measured ST-elevation values. The optimal cut-off point was 1.15 mm (sensitivity 89%, specificity 98%) for the computer program in detecting manually measured ST elevation ≥2 mm, and 0.45 mm (sensitivity 74%, specificity 99%) in revealing manual ST elevation ≥1 mm (**I**). Using an expert

electrocardiographer's anatomical interpretation as the gold standard, the computer model recognized patients fulfilling ECG criteria for any occlusion of the LAD with a specificity of 99% and a sensitivity of 67% (κ=0.71). Proximal LAD occlusion was detected with 100% specificity and 86% sensitivity (κ=0.72). The computer program detected a distal occlusion in the LAD with a specificity of 99% and a sensitivity of 40% (κ=0.72) (**II**). ST elevation ≥0.5 mm in lead aVL or any ST elevation in lead aVR in association with precordial ST-segment elevation in at least two contiguous leads (including V_2, V_3 or V_4) had a sensitivity of 94%, specificity 49%, positive predictive value 85% and negative predictive value 71% in predicting a proximal LAD lesion (**III**). We used a composite of death, clinical re-infarction or disabling stroke as the overall end-point event at a median 2.7 year follow-up (**III, IV**). ECG or angiographic signs of lesion proximality were not associated with poorer outcome at day 30 or 2.7 year follow-up (**III**). A higher overall event rate was observed in the EMI group compared to the PIS group (11.4 [9.4-13.9] and 6.9 [6.0-8.0] per 100 person-years, respectively, RR 1.6, p<0.001). The EMI pattern was independently predictive of adverse outcome in multivariable analysis (HR 1.52, CI 1.01-2.30, p=0.04). The PIS pattern (n=952) was associated with a lower overall event rate in patients treated with primary PCI compared with FT (5.5 [4.4-6.9] and 8.5 [7.0-10.4] per 100 person-years, respectively, RR=0.6, p=0.004). No significant difference in outcome between treatment strategies was observed in the EMI group as a whole. However, in patients with anterior EMI without ECG signs of reperfusion, the superiority of primary PCI was reflected in a 51% reduction in the relative risk of composite end point (p=0.008) (**IV**).

In conclusion, automatically measured ST-segment deviations were smaller than those measured manually. Correction should be made to obtain optimal results in automated analysis of the ECG, as the results have important implications for clinical decision-making. When the ECG findings were evaluated against coronary angiography obtained at the acute phase, the site of occlusion in the LAD could be reliably predicted by 12-lead ECG in patients with acute anterior MI. Using corrected cut-off points for the computer program to detect equivalents of manual ST elevations, computerized anatomical interpretation of the ECG is feasible and allows detection of a proximal LAD occlusion with excellent accuracy. However, the prognostic significance of the level of occlusion in the LAD in the modern era of acute STEMI treatment should be reassessed. More detailed ECG analysis, involving also Q and T wave morphology, is useful for rapid identification of high-risk patients, for whom every effort should be made to arrange transportation for primary PCI, or vice versa, in order to identify low-risk patients for whom FT might be an alternative option.

TIIVISTELMÄ (Abstract in Finnish)

Sydämen ST-nousuinfarktin hoito kohdistuu veren virtauksen palauttamiseen tukossa olevassa sepelvaltimossa joko laskimonsisäisellä liuotushoidolla tai välittömällä pallolaajennuksella. Välitön pallolaajennus ei ole mahdollista kaikkina vuorokauden aikoina kuin osassa sairaaloita, siksi on tärkeää kyetä tunnistamaan suuren vaaran potilaat. Nopea diagnoosin tekeminen, yksilöllinen riskinarvio ja veren virtauksen palauttamiseen tähtäävän hoidon valinta pohjautuu ensi vaiheessa sydänsähkökäyrässä (EKG) nähtäviin muutoksiin. Apuna voidaan käyttää automaattisia EKG:n tulkintaohjelmia. Tietokonepohjaisten analyysiohjelmien osuvuutta tulisi testata ihmisten tekemiin analyyseihin. Vasemman eteen laskevan sepelvaltimon (LAD) tyvialueen tukkeutumisen on osoitettu liittyvän huonoon ennusteeseen, siksi se tulisi tunnistaa EKG:n avulla. Sydänlihaksen hapenpuutteen kestosta saadaan tietoa EKG:n avulla. ST-välin nousu ilman Q-aaltoja tai T-aallon inversiota, pre-infarction syndrome (PIS), viittaa hyvin tuoreeseen tukokseen. ST-välin nousu yhdistettynä Q-aaltojen esiintymiseen ja/tai T-aallon kääntymiseen negatiiviseksi puolestaan viittaa sydänlihaskuolioon ja/tai hapenpuutteen väistymiseen (evolving myocardial infarction, EMI).

Väitöskirjatyön tavoitteena oli verrata J-pisteestä, ST-välistä ja T-aallosta mitattujen EKG-tulkintojen keskinäistä osuvuutta tietokoneohjelman ja kardiologin välillä (**I**); kehittää tietokoneavusteinen EKG:n tulkintaohjelma tunnistamaan LAD:n tyvialueen tukoksen aiheuttama sydäninfarkti (**II**); selvittää EKG:lla ja sepelvaltimoiden varjoainekuvauksella arvioidun LAD:n tukoskohdan vaikutus pitkäaikaisennusteeseen liuotushoidolla tai välittömällä pallolaajennuksella hoidetuilla sydäninfarktipotilailla (**III**); tutkia hapenpuutteen kestoa kuvaavien EKG-muutosten (PIS ja EMI) merkitystä liuotushoidon ja pallolaajennushoidon valinnassa (**IV**).

Osatutkimusten **I** ja **II** perusjoukko koostui 531 perättäisestä potilaasta, jotka tulivat ensiapuun epäillyn sepelvaltimotautikohtauksen vuoksi. Osatutkimuksissa **III** ja **IV** oli mukana 1522 ST-nousuinfarktiin sairastunutta potilasta, jotka oli sokkoutettu joko liuotus- tai pallolaajennushoitoryhmään.

Bland-Altmanin analyysi osoitti, että tietokoneohjelman ja kardiologin tekemien mittaustulosten keskinäinen osuvuus oli hyväksyttävää J-pisteestä ja T-aallosta mitattuna, mutta ei ST-välin osalta. Tietokonemittaus tuotti systemaattisesti pienempiä ST-nousulukemia kuin

kardiologin käsin suorittama mittaus. Paras mahdollinen raja-arvo ≥2mm:n ST-nousun tunnistamiseksi tietokonemittauksessa oli 1.15 mm (sensitiivisyys 89%, spesifisyys 98%) ja ≥1 mm:n ST-nousun tunnistamiseksi 0.45 mm (sensitiivisyys 74%, spesifisyys 99%) (**I**). Kun automaattista EKG-analyysiä verrattiin kardiologin tekemään anatomiseen EKG:n tulkintaan, tietokoneohjelma kykeni tunnistamaan LAD:n tukoksen 99% spesifisyydellä ja 67% sensitiivisyydellä (κ=0.71). LAD:n tyvialueen tukoksen tietokoneohjelma tunnisti 100% spesifisyydellä ja 86% sensitivisyydellä (κ=0.72) (**II**). ST-nousu ≥0.5 mm kytkennässä aVL tai minkä asteinen ST-nousu tahansa kytkennässä aVR yhdistettynä samanaikaiseen ST-segmentin nousuun vähintään kahdessa vierekkäisessä rintakytkennässä V_2, V_3 tai V_4 osoitti myöhemmin varjoainekuvauksessa varmistuneen LAD:n tyvialueen tukoksen 94% sensitiivisyydellä, 49% spesifisyydellä, 85% positiivisella ennustearvolla ja 71% negatiivisella ennustearvolla (**III**). Osatutkimuksissa **III** ja **IV** päätetapahtumana oli kuoleman, uusinta sydäninfarktin tai aivoinfarktin yhdistelmä 2.7 vuoden seuranta-aikana. EKG:lla tai varjoainekuvauksella todettu LAD:n tyvialueen tukos ei ollut yhteydessä huonoon ennusteeseen seuranta-aikana (**III**). Päätetapahtumia oli enemmän EMI- kuin PIS-ryhmässä (11.4 [9.4-13.9] ja 6.9 [6.0-8.0] 100 henkilövuotta kohden vastaavassa järjestyksessä, RR 1.6, p<0.001). Monimuuttuja-analyysissa EMI oli päätetapahtuman itsenäinen riskitekijä (HR 1.52, CI 1.01-2.30, p=0.04). PIS-ryhmässä (n=952) välittömällä pallolaajennuksella hoidetuilla potilailla päätetapahtumia ilmaantui seuranta-aikana vähemmän kuin liuotushoidetuilla (5.5 [4.4-6.9] ja 8.5 [7.0-10.4] 100 henkilövuotta kohden vastaavassa järjestyksessä, RR=0.6, p=0.004). Kokonaisuudessaan EMI-ryhmän sisällä ei ollut eroa hoitoryhmien välisessä ennusteessa. Kuitenkin potilailla, joilla EKG:ssa todettiin etuseinän EMI ilman merkkiä tukossuonen avautumisesta, välitön pallolaajennus vähensi päätetapahtumia seuranta-aikana 51% liuotushoitoon verrattuna (p=0.008) (**IV**).

Yhteenveto: Tietokoneohjelman ja käsin mitatun ST-segmentti heilahduksen ero tulisi huomioida tietokoneavusteisissa EKG-ohjelmissa, koska tuloksilla on tärkeä merkitys kliinisessä päätöksenteossa. Etuseinän ST-nousuinfarktissa EKG:n avulla kyetään luotettavasti ennustamaan LAD:n tukoksen sijainti. ST-nousuinfarktin nykyaikaisen hoidon aikakaudella, LAD:n tyvialueen tukoksen ennusteellinen merkitys täytyy arvioida uudelleen. ST-nousun sekä Q- ja T-aaltojen morfologian yksityiskohtainen arviointi auttaa tunnistamaan suuren riskin omaavat potilaat nopeasti. Suuren riskin potilaat tulisi kuljettaa sairaalaan, jossa voidaan tehdä välitön pallolaajennushoito. Vastavuoroisesti, EKG auttaa tunnistamaan ne matalan riskin ST-nousuinfarkti potilaat, joiden kohdalla liuotushoito on hyvä vaihtoehto.

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ABBREVIATIONS

κ	kappa
ΣST	sum ST-segment deviation
ACS	acute coronary syndrome
AMI	acute myocardial infarction
CI	confidence interval
DANAMI-2	the Danish Trial in Acute Myocardial Infarction-2
ECG	electrocardiogram
EMI	evolving myocardial infarction
FT	fibrinolytic therapy
GI	grade of ischemia
HR	hazard ratio
IQ	inter-quartile
ICH	intracranial hemorrhage
IRA	infarct-related artery
LAD	left anterior descending coronary artery
LBBB	left bundle branch block
LCX	left circumflex coronary artery
LD	left diagonal
LV	left ventricle
LVH	left ventricular hypertrophy
MI	myocardial infarction
NPV	negative predictive value
NSTEMI	non-ST-elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
PIS	pre-infarction syndrome
PPV	positive predictive value
PTCA	percutaneous transluminal coronary angioplasty
RBBB	right bundle branch block
RCA	right coronary artery
RR	relative risk
rt-PA	recombinant tissue plasminogen activator
RV	right ventricle
RVI	right ventricular infarction
STEMI	ST-elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction

LIST OF ORIGINAL COMMUNICATIONS

This dissertation is based on the following four original publications, referred to in the text by their Roman numerals **I-IV**.

I Eskola MJ, Nikus KC, Voipio-Pulkki L-M, Huhtala H, Parviainen T, Lund J, Ilva T, Porela P (2005): Comparative accuracy of manual versus computerized electrocardiographic measurement of J-, ST- and T-wave deviations in patients with acute coronary syndrome. Am J Cardiol 96:1584-1588.

II Eskola MJ, Nikus KC, Voipio-Pulkki L-M, Huhtala H, Lund J, Ilva T, Niemelä KO, Porela P (2007): Detection of proximal coronary occlusion in acute coronary syndrome: a feasibility study using computerized electrocardiographic analysis. Ann Noninvasive Electrocardiol 12:301-305.

III Eskola MJ, Nikus KC, Holmvang L, Sclarovsky S, Tilsted HH, Huhtala H, Niemelä KO, Clemmensen P (2007): Value of the 12-lead electrocardiogram to define the level of obstruction in acute anterior wall myocardial infarction: correlation to coronary angiography and clinical outcome in the DANAMI-2 trial. Int J Cardiol doi:10.1016/j.ijcard.2007.10.035

IV Eskola MJ, Holmvang L, Nikus KC, Sclarovsky S, Tilsted HH, Huhtala H, Niemelä KO, Clemmensen P (2007): The electrocardiographic window of opportunity to treat vs. the different evolving stages of ST-elevation myocardial infarction: correlation with therapeutic approach, coronary anatomy, and outcome in the DANAMI-2 trial. Eur Heart J 28:2985-2991.

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INTRODUCTION

Recent developments in therapeutic options for acute ST-elevation myocardial infarction (STEMI) call for early risk stratification in order to select treatment strategies appropriate for individual patients. A variety of scores have been used as tools to guide decisions regarding reperfusion therapy (Wilkins et al. 1995, Morrow et al. 2000, Thune et al. 2005). To be practical clinically, a risk stratification tool should be simple and easy to apply, as is for example the electrocardiogram (ECG). The ECG is still the most readily available and fastest method for the diagnosis of STEMI and thus crucial to rapid therapeutic decision-making in the acute phase. The current trend is for 12-lead ECGs to be recorded by paramedics in the field, and transmitted via cellular telephone or fax to the target emergency department. ECG interpretation is also often made by paramedics in out-of-hospital settings, which means that computer-based interpretation programs could be ideal. Acute or evolving changes in the ST-T waveforms and the Q-waves potentially allow the clinician to identify the probable infarct-related artery (IRA), to estimate the extent of myocardium at risk and to evaluate the dynamic process of myocardial ischemia.

Percutaneous coronary intervention (PCI) refers to a group of invasive procedures designed to improve blood flow to the myocardium through re-canalization of diseased coronary arteries. Interventions currently used in clinical practice include plain old balloon angioplasty, intracoronary stenting and thrombectomy. Several studies have shown that primary PCI is preferable to intravenous fibrinolysis for the treatment of STEMI (Grines et al. 1993, Zijlstra et al. 1993, The global use of strategies to open occluded coronary arteries in acute coronary syndromes (GUSTO IIb) angioplasty substudy investigators 1997, Weaver et al. 1997, Andersen et al. 2003b, Keeley et al. 2003, Steg et al. 2003, Widimsky et al. 2003). Consequently, current guidelines recommend primary PCI as the treatment of choice whenever feasible (Van de Werf et al. 2003).

There is still no consensus as to whether all STEMI patients benefit from an invasive strategy (Brophy and Bogaty 2004). In practice, the choice between fibrinolytic therapy (FT) and primary PCI depends on factors such as physician preferences, availability of infrastructure, economic considerations and time of admission, rather than clinical evidence. The report on the use of primary PCI from the Global Registry of Acute Coronary Events (GRACE) showed that 27% of patients with acute STEMI were treated with primary PCI and 47% received FT (Fox et al. 2003). In a global perspective most patients are treated in hospitals without 7-days-a-week

and 24-hours-a-day cardiac catheterization facilities. Also in Finland, invasive treatment is available around the clock in only two hospitals. Building up around-the-clock invasive systems is a considerable logistic and economic challenge. It may be most useful to view FT and primary PCI as complementary rather than competitive (Brophy and Bogaty 2004). It would thus be of vital importance to be able to define high-risk patients for whom every effort should be made to transfer for primary PCI, or vice versa, to define low-risk patients for whom FT might be an alternative option. It is conceivable that the first-line ECG interpreter will be involved in triaging patients in the pre-hospital phase to hospitals offering primary PCI, and here the ECG is the most valuable tool for patient selection.

One purpose in this thesis was to develop and validate a computer model for anatomical interpretation of the ECG. We investigated the value of the ECG in identifying the left anterior descending coronary artery (LAD) as the IRA and the impact on clinical outcome of the ECG and of angiographic signs of proximal versus distal LAD occlusion. Special focus was on the prognostic value of the 12-lead ECG patterns of the pre-infarction syndrome (PIS) and evolving myocardial infarction (EMI) with respect to reperfusion strategy in patients with acute STEMI.

REVIEW OF THE LITERATURE

1. ST-elevation myocardial infarction

1.1 Definition

Myocardial ischemia is the result of an imbalance in perfusion between supply and demand. Irreversible ischemic myocardial cell injury develops in an increasing number of cells as the duration of coronary occlusion is prolonged. In experimental animals, irreversible myocardial injury has been shown to occur when perfusion is interrupted completely for intervals as brief as 20-60 minutes (Reimer et al. 1977, Bergmann et al. 1982). Complete necrosis of all myocardial cells at risk requires at least 2-4 hours or longer depending on the presence of collateral circulation to the ischemic zone, persistent or intermittent coronary arterial occlusion, the sensitivity of the myocytes to ischemia, pre-conditioning, and/or, finally, the individual demand for myocardial oxygen and nutrients (Thygesen et al. 2007).

Myocardial infarction (MI) is defined by pathology as myocardial cell death due to prolonged ischemia. The condition is diagnosed when blood levels of sensitive and specific biomarkers (preferably troponin) are increased in the clinical setting of acute myocardial ischemia (Albert and Thygesen 2000). Possible ischemic symptoms include various combinations of chest, upper extremity, jaw or epigastric discomfort upon exertion or at rest. The discomfort associated with acute myocardial infarction (AMI) usually lasts at least 20 minutes. Often the discomfort is diffuse, not localized, not positional, not affected by movement of the region, and it may be accompanied by dyspnoea, diaphoresis, nausea or syncope. Myocardial infarction may occur with atypical symptoms, or even without symptoms, being detectable only by ECG, biomarkers or cardiac imaging (Thygesen et al. 2007).

The different presentations of acute coronary syndromes (ACS) share a common pathophysiological substrate. The major symptom which initiates the diagnostic and therapeutic decision-making process is chest pain, while the initial classification of patients is based on the ECG. Two categories of patients may be encountered. Firstly, those with typical acute chest pain and persistent (>20 minutes) ST-segment elevation - this is termed ST-elevation ACS, and

generally reflects an acute total coronary occlusion. Most of these patients will ultimately develop a STEMI. The therapeutic objective here is to achieve rapid, complete and sustained reperfusion by primary PCI or FT. The second category comprises patients with acute chest pain but without persistent ST-segment elevation. These have rather persistent or transient ST-segment depression or T-wave inversion, flat T waves, pseudo-normalization of T waves or no ECG changes at presentation. The initial strategy in such cases is to alleviate ischemia and symptoms, to monitor the patient with serial ECGs and to repeat measurements of markers of myocardial necrosis. At presentation, the working diagnosis of non-ST elevation ACS, based on the measurement of troponins, will be further specified as non-ST elevation MI (NSTEMI) or unstable angina. (Bassand et al. 2007)

1.2 Prognosis

There would appear to be some discrepancy in the reported mortality of STEMI patients between prospective randomized clinical studies, registries and unselected cohorts. A meta-analysis of 23 randomized trials comparing primary PCI with FT showed a short-term mortality (4-6 weeks) of 7 to 9% and a long-term mortality (6–18 months) of 10 to 13%, respectively (Keeley et al. 2003). These figures are certainly higher in all-comers. In-hospital mortality rates for participants in clinical trials of FT are lower (7%) than for non-participants (17%), ($p<0.001$) (Jha et al. 1996). In Finland, an in-hospital mortality of 9.6% has been reported in prospectively collected consecutive patients with STEMI admitted to a university hospital (Nikus et al. 2007). From the Swedish Register of Cardiac Intensive Care, a substantially different 1-year mortality among STEMI trial participants versus non-participants has been reported 8.8 vs. 20.3%, ($p<0.001$) (Bjorklund et al. 2004). Even after adjustment for a number of risk factors, 1-year mortality was still twice as high in non-trial compared with trial patients. This is in concord with the 20.5% 1-year mortality of STEMI patients reported by Terkelsen and associates (2005) and 19.2% at a mean follow-up of 10 months in the afore-mentioned study by Nikus and group (2007).

1.3 Risk stratification of patients

Immediate risk stratification in the emergency room or preferably by paramedics in out-of-hospital settings is an important step for the appropriate management of patients. The clinical

determinants of mortality in patients treated with FT within 6 hours of symptom onset are multifactorial and the relations complex. Although a few variables contain most of the relevant prognostic information, many others contribute additional independent prognostic data. For the 41 021 patients enrolled in GUSTO-I, a randomized trial of four fibrinolytic strategies, relations between clinical descriptors routinely collected at initial presentation and death within 30 days (which occurred in 7% of cases) were examined. Multivariable analysis identified age as the most significant determinant of 30-day mortality, ranging from 1.1% in the youngest decile (<45 years) to 20.5% in patients >75 ($p<0.001$). Other factors strongly associated with increased mortality were lower systolic blood pressure, higher Killip class, elevated heart rate and anterior infarction. Together, these five characteristics contained 90% of the prognostic information in the baseline clinical data (Lee et al. 1995).

1.3.1 TIMI risk score

The Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI was created as a simple arithmetic sum of independent predictors of 30-day mortality weighted according to the adjusted odds ratios from logistic regression analysis in the Intravenous nPA for Treatment of Infarcting Myocardium Early II (InTIME II) trial (n=14 114) (Morrow et al. 2000). Ten characteristics accounted for 97% of the predictive capacity of the multivariable model and were selected for inclusion in the TIMI risk score for STEMI. This score was calculated as the sum of point values (range 1-3) assigned to each risk factor: age (3 points for ages ≥75 years, 2 points for age 65-74), Killip class >I (2 points), heart rate >100 beats per minute (2 points), anterior MI or left bundle branch block (LBBB) (1 point), systolic blood pressure <100 mmHg (3 points), time to thrombolysis >4 hours (1 point), weight <67 kg (1 point), diabetes or history of hypertension or prior angina (1 point). The TIMI risk for STEMI showed a strong association with mortality at 30 days, with a >40-fold graded increase in mortality between those with a risk score of 0 and those with a score >8 ($p<0.0001$). The discriminatory capacity of the model remained good for prediction of 1-year mortality among 30-day survivors.

Risk stratification on admission based on the TIMI risk score identifies a group of high-risk patients who have a significantly reduced mortality with an invasive strategy of primary PCI compared to FT. Judging from data from the landmark Danish Trial in Acute Myocardial Infarction-2 (DANAMI-2) study, for patients classified as low risk (TIMI risk score 0 to 4) there was no difference in 3-year mortality between the two treatment arms (primary PCI 8.0 vs. FT

5.6%, respectively, p=0.11). In the high-risk group (TIMI risk score ≥5) there was reduction in mortality with primary PCI compared to FT (25.3 vs. 36.2%, respectively, p=0.02) (Thune et al. 2005). When re-infarction was used as end-point, there was a significant reduction in events in the low-risk group with primary PCI compared to FT (6.6 vs. 10.4%, respectively, p=0.02), whereas in the high-risk group the re-infarction rate was similar between the treatment strategies (10.2 vs. 13.5%, respectively, p=0.18).

2. ECG presentations in acute STEMI

The ECG is not only the oldest but in fact, over 100 years after its introduction, continues to be the most commonly used cardiovascular laboratory procedure. One of the most useful contributions of the ECG is in the evaluation of ischaemic heart disease, especially AMI. In 1912 Herrick described the features of what was ultimately shown to be coronary occlusion (Herrick 1912). He also suggested that coronary occlusion is not always fatal. In 1918 Smith described ECG changes in experimental coronary occlusion in a dog model and stressed the similarities between the findings in canines and humans (Smith 1918). In a case report in 1920 Pardee described ST-segment elevation in leads II and III with progressive T-wave inversion over a period of time with return of the ST to isoelectric level (Pardee 1920). By the year 1930 the importance of the ECG in the recognition of MI was realized and accepted by the medical profession.

The ECG evinces a well-established temporal course of development in STEMI patients. The earliest ECG finding is the tall and peaked, hyperacute T wave. At this stage, the R wave also increases in size by combining with the elevated ST segment, particularly in anterior distribution. As the infarction progresses, the ST-segment elevation assumes a more typical morphology, with a usually either convex or flat initial upsloping portion of the ST segment. The R wave diminishes and may be lost entirely with the development of the Q wave (Brady et al. 2001). More recently, a new ECG classification has been proposed, the grade of ischemia (GI), based on changes evolving during ischemia and reperfusion, and including the terminal QRS complex (Birnbaum and Sclarovsky 2001a).

The ECG is the first test performed when AMI is suspected, its contribution being not only to the diagnosis of infarction but also to early risk stratification and clinical management.

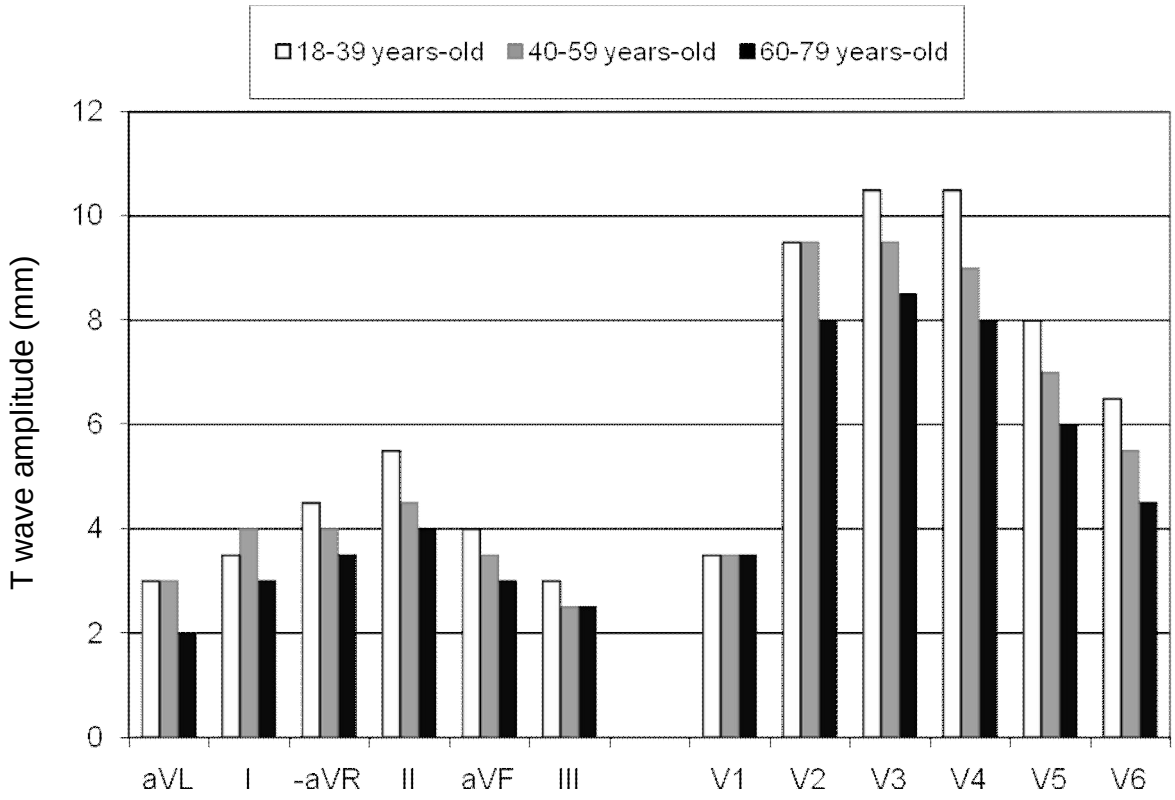
2.1 T wave

Ventricular repolarization produces the T wave. No widely accepted criteria exist regarding normal values for T wave amplitude. According to a study by Gambill and associates (1995) there were three general trends in T wave amplitudes in normal populations. First, normal T wave amplitudes were greater in the precordial than in the limb leads. Second, normal T wave amplitudes were greater in men than in women in both limb and precordial leads. The third general trend was for the normal T wave amplitudes to be inversely proportional to age. The distribution of the normal T wave amplitude is shown in Figure 1. Suggested criteria for the normal size of the T wave are at least $\frac{1}{8}$ but less than $\frac{2}{3}$ of the amplitude of the corresponding R wave, and the height of the T wave <10 mm (Channer and Morris 2002).

Transient tall and peaked T waves represent a first manifestation of acute ischemia in the case of sudden complete occlusion of the epicardial coronary artery (Smith 1918). In patients in whom negative T waves develop, episodes of re-ischemia often manifest a transient return of the inverted T wave to the upright configuration in the ischemic region (pseudonormalization), with or without ST-segment elevation (Wasserburger and Corliss 1965, Noble et al. 1976, Zack et al. 1987).

2.2 ST segment

The QRS complex terminates at the J point. The ST segment lies between the J point and the beginning of the T wave, and represents the period between the end of ventricular depolarization and the beginning of repolarization. Normally, the ST-segment on the ECG is at approximately the same baseline level as the PR and TP segments (isoelectric line) (Wagner and Lim 2008). Textbooks of electrocardiography discuss the relative merits of measuring the ST segment relative to the PR or TP segment and generally agree that the PR segment is best in determining isoelectricity. However, the PR segment may be depressed by the atrial repolarization wave (Ta wave) and the ST segment may be superimposed on a depressed Ta wave. This may result in less ST-segment elevation when measured relative to the TP segment than when measured relative to the PR segment. In some cases there is no TP segment evident (e.g., during tachycardia), and the PR segment is then considered the isoelectric line (Berry et al. 1989, Mizutani et al. 1990). In clinical studies, both the PR and TP segments have been used as the isoelectric line by different



F**igure 1.** The normal T wave amplitudes (mm) for the different age groups are presented. The order of the leads is presented according to Cabrera. Modified from the study by Gambill et al. (1995).

authors. ST-segment deviation is the amplitude (mm) of the ST-segment displacement from the isoelectric line measured at different time-points, i.e. at the J point and at 20-80 ms after it.

Myocardial ischemia is seen as ST-segment elevation on the surface ECG in leads facing the ischemic area. When a sudden, complete occlusion of a coronary artery prevents blood flow from reaching an area of the myocardium, the resulting epicardial injury is manifested by a deviation of the ST segment toward the involved region (Vincent et al. 1977, Kleber et al. 1978, Janse et al. 1979). Transient or new persistent ST-segment elevation manifests an acute regional transmural ischemia surrounded by healthy myocardium. ST segments on the surface ECG change within seconds of coronary artery occlusion (Krucoff et al. 1990). This is also seen during brief therapeutic balloon occlusion with percutaneous transluminal coronary angioplasty (PTCA) (Wagner et al. 1988). Many factors, for example myocardial mass, distance between electrodes and ischemic zone, reciprocal changes and attenuation of opposite ischemic vectors, may affect the magnitude of ST elevation.

The ST-segment elevation differs according to the method of measurement, with ST segment amplitude uniformly and statistically significantly higher when measured at 60 ms after the J point than when measured at the J point (Smith 2006). Measuring the ST-segment deviation at 60 ms after the J point may increase the sensitivity of ST-segment elevation in detecting total coronary occlusion. However, this may result in more false-positive ST changes, indicating myocardial ischemia when there is none. When the 80 ms measurement point is used, greater specificity is achieved (Tisdale and Drew 1993). In a consensus statement the recommended selection of the measurement point for ST-segment monitoring in patients with ACS is J+60 ms (Drew and Krucoff 1999). Recent guidelines for a universal definition of MI recommend measurement of the ST-segment deviation from the J point (Thygesen et al. 2007).

The ECG criterion for the diagnosis of acute STEMI is a new ST elevation in two contiguous leads with cut-off points ≥2 mm in men or ≥1.5 mm in women in leads V_2-V_3 and/or ≥1 mm in other leads in the absence of left ventricular hypertrophy (LVH) and LBBB. Contiguous leads constitute lead groups such as anterior leads (V_1-V_6), inferior leads (II, III, aVF) or lateral leads (I, aVL) (Thygesen et al. 2007). Nevertheless, there are several conditions other than STEMI which may present with ST elevation and need immediate recognition to avoid false treatment (Wang et al. 2003). These include e.g. LVH, early repolarization, Prinzmetal's angina, chronic left ventricular aneurysm, acute pericarditis, pulmonary embolism, the Brugada syndrome, severe hyperkalemia and hypercalcemia. Moreover, studies have indicated that in a healthy population, 91% of men between the ages of 16 and 58 years evince ST-segment elevation of 1 to 3 mm in one or more of the precordial leads, mainly in lead V_2 (Hiss et al. 1960). The prevalence of these changes declines with age, reaching 14% in the oldest males, whereas in females the prevalence is distributed similarly at about 20% from puberty to advanced age (Surawicz and Parikh 2002). The normal limits of the ST amplitude in healthy individuals have been found to be lower in women than in men, particularly in the precordial leads. For example, when the 96^{th} percentile ranges of normal were estimated by excluding 2% of measurements at the extremes of a range of values, the upper limit of normal ST amplitude in V_3 in a 25-year-old man was 3.1 mm but only 1.1 mm in a woman of the same age (Macfarlane 2001).

2.3 Localization of infarction

The location of the ischemic zone during AMI is established by evaluating the ST-segment deviation in different leads. It is important to identify the anatomic location of a threatening acute MI to estimate the amount of jeopardized myocardium and to determine the relative risk of morbidity and mortality. The most frequently used terminology is summarized in Table 1.

Table 1. Anatomic location correlated with ECG leads and ST-segment deviation.

Anatomic location	**Involved ECG leads**	**ST-segment finding**
Anterior wall	V_1-V_4	Elevation
Inferior wall	II, III, aVF	Elevation
Lateral wall	I, aVL, V_5-V_6	Elevation
Posterior wall	V_1-V_2/V_7-V_9	Depression/elevation
Right ventricle	V_4R	Elevation

2.4 Reciprocal changes

Reciprocal change is defined as ST depression in leads separate and distinct from leads reflecting ST elevation. Patients who have ST elevation in one area often have ST depression in others. The accompanying ST deviation may represent ischemia in a myocardial region other than that of the infarction (ischemia at a distance) or may represent pure reciprocal changes (a benign electrical phenomenon). There is abundant literature on the significance of different types of ST depressions during STEMI (Becker and Alpert 1988). Most of the common patterns of remote ST depression probably represent benign reciprocal changes and not ischemia at a distance (Celik et al. 2003).

In anterior STEMI, ST depression in the inferior leads (II, III, aVF) is reciprocal to involvement of the basal anterolateral region, which is supplied by the first diagonal (LD) side branch and is represented in the ECG by ST-segment elevation in high lateral leads I and aVL (Birnbaum et al. 1994, Sclarovsky et al. 1994). Thus, ST depression in the inferior leads during acute anterior STEMI indicates injury to the high anterolateral wall and not inferior wall ischemia (Haraphongse et al. 1984, Fletcher et al. 1993).

In patients with inferior STEMI, an ST depression in lead aVL is a pure reciprocal change and is found in almost all patients (Birnbaum et al. 1993b). In cases with inferior STEMI, ST depression in leads V_1-V_3 probably does not represent ischemia at a distance but rather reciprocal changes caused by posterior, inferoseptal, apical or lateral left ventricular involvement (Gibson et al. 1982, Ong et al. 1983, Ruddy et al. 1986). In contrast, among patients with inferior STEMI, ST-segment depression in leads V_4-V_6 is associated with concomitant LAD coronary artery stenosis and three-vessel disease (Strasberg et al. 1990, Hasdai et al. 1997, Birnbaum et al. 1999). Accordingly, in inferior STEMI, the presence of a non-reciprocal pattern of ST depression (present in ECG leads not anatomically opposite to the infarct area), may signify ischemia at a distance.

It has been reported that in patients with NSTEMI, isolated ST-segment depression in leads V_1-V_4 is more likely to be caused by posterior wall STEMI (reciprocal changes) when it is associated with positive T waves (Boden et al. 1987). It has since been found that the polarity of the T waves in the precordial leads with ST depression cannot be used to differentiate between two etiologies of ST depression (Porter et al. 1998).

2.5 Attenuation phenomenon

If the ischemia involves opposite areas of the myocardium, two injury vectors are generated. Owing to the opposite orientation of these vectors, the signs of ischemia in both areas may be blunted. Moreover, the reciprocal changes normally present in the non-ischemic opposite myocardial segments will be affected. Here the term attenuation phenomenon is used (Sclarovsky 1999a). The attenuation phenomenon is possible in infarctions in all major coronary arteries. For example, the LAD artery may supply two electrically opposite areas, the basal anterolateral wall (lead I, aVL) and the inferior wall (lead III). Also a proximal occlusion of the left circumflex coronary artery (LCX) produces ischemia in opposite areas such as the anterolateral and inferoposterior. In inferior STEMI caused by proximal right coronary artery (RCA) occlusion with concomitant right ventricular infarction (RVI), posterior wall injury may be masked because two opposed electrical vectors may cancel each other out. Thus transmural ischemia of the posterior wall generating a posteriorly directed injury vector ("mirror-image MI": ST depression in leads V_1-V_3) and concomitant transmural ischemia of the right ventricle (RV), generating an anterior injury vector, may result in a net effect of minor ST changes or

even an isoelectric ST segment. Transmural ischemia confined to the RV, on the other hand, may show ST elevations in leads V_1-V_3 (Lew et al. 1985).

2.6 Grade of ischemia

The grade of ischemia (GI), the Sclarovsky-Birnbaum grade, for application on the presenting ECG, estimates the severity of the ischemia/infarction process (Sclarovsky et al. 1990, Birnbaum and Sclarovsky 2001a). The approach is based on the concept that the severity of the ischemia/infarction process is determined by the degree of myocardial protection provided by the combination of collateral vessels and ischemic preconditioning.

The ischemia grading system consists of three grades (Birnbaum and Sclarovsky 2001a). Grade 1: tall upright T waves without ST-segment elevation; Grade 2: ST-segment elevation in ≥2 adjacent leads without terminal QRS distorsion; and Grade 3: ST-segment elevation with distorsion of the QRS complex in ≥2 adjacent leads defined as disappearance of the S wave in leads V_1-V_3 (QRS complex with Rs configuration) or appearance of ST-segment elevation measured at the J point at ≥50% of the R wave amplitude in the other leads (qR configuration) (Figure 2).

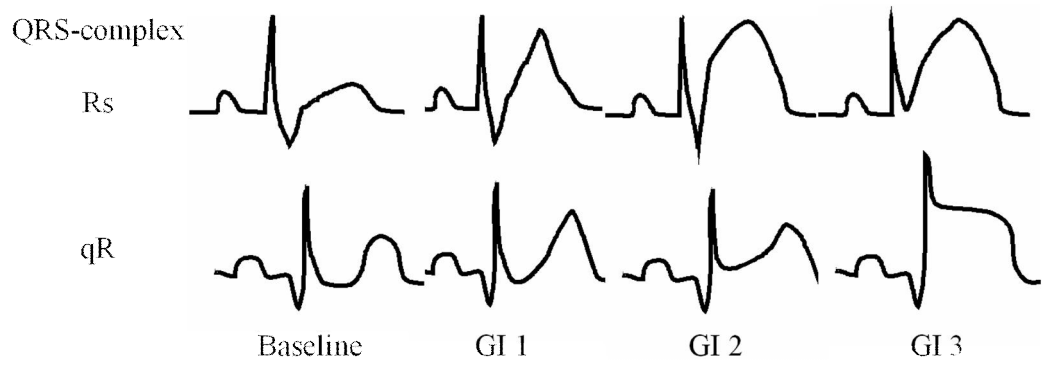


Figure 2. Baseline ECG and the grades of ischemia (GI) in the different types of QRS-complexes, see text. Modified from Birnbaum and Sclarovsky (2001a).

The changes in the GI 3 include an increase in the amplitude of the R waves and disappearance of the S waves. These changes in the terminal portion of the QRS are explained by prolongation of the electrical conduction in the Purkinje fibres in the ischemic region (Holland and Brooks 1976, David et al. 1982). The delayed conduction reduces the degree of

cancellation, resulting in an increase in R wave amplitude in leads with a terminal R wave and a decrease in the S wave amplitude in leads with a terminal S wave on the surface ECG (Holland and Brooks 1976, David et al. 1982, Barnhill et al. 1989, Wagner et al. 1988). The Purkinje fibres are less sensitive to ischemia than the contracting myocytes (Dehaan 1961). Hence, for an alteration in the terminal portion of the QRS to occur, there should probably be a severe and prolonged ischemia affecting Purkinje fibres (Holland and Brooks 1976). In patients with collateral circulation no changes have been detected in the QRS complex during PTCA (Spekhorst et al. 1990). Thus the absence of distorsion of the terminal portion of the QRS, despite prolonged ischemia, may be a sign of myocardial protection by persistent myocardial flow either by antegrade or collateral circulation.

2.7 Dynamic ECG changes during reperfusion and infarct process

The ECG recorded during acute ischemia as well as during the ensuing recovery phase is an objective reflection of the series of events which occur in the myocardium. Sclarovsky has defined the stages of the dynamic ischemic process by two distinct ECG patterns: the pre-infarction syndrome (PIS) and evolving MI (EMI) (Sclarovsky 1999a, Sclarovsky 1999b). These patterns reflect the myocardial response to acute ischemia and reperfusion and to the infarctation of the jeopardized myocardium.

2.7.1 T wave

As the jeopardized myocardium either recovers or infarcts, the positive T waves generally migrate past the isoelectric line (Mandel et al. 1968). Typically, the terminal portion of the T wave is the first to become inverted, followed by the middle and initial portion. Early inversion of the T waves after FT indicate a better degree of reperfusion (Richardson et al. 1988, Matetzky et al. 1994), as is seen after deflation of the balloon during PTCA (Mager et al. 1991). The rapidity and depth of T-wave inversion is associated with IRA patency as assessed by the angiogram (Oliva et al. 1993). The early development of terminal T-wave inversion as a marker of a patent IRA has a sensitivity of 63%, specificity of 94%, positive predictive value (PPV) of 96% and negative predictive value (NPV) of 50% (Doevendans et al. 1995).

Negative T waves in the early phase of STEMI have been associated with improved patient outcome related to an open IRA, restored myocardial blood flow, reappearance of the R wave and better left ventricular function (Doevendans et al. 1995, Agetsuma et al. 1996, Porter et al. 2000). T-wave evolution in ischemic heart disease is not a marker of cell death, but is instead caused by changes in the ion channels in regions of the heart that remain viable after an episode of severe ischemia (Katz 2006).

2.7.2 ST segment

The changes in the ST segment which are prominent during epicardial injury typically disappear when the jeopardized myocardium either infarcts or is salvaged. It has been established that after coronary reperfusion there is rapid resolution of ST-segment elevation (Anderson et al. 1983, Ganz et al. 1984). ST resolution after reperfusion therapy is an excellent indicator for prognosis and recovery of left ventricular function, as it assesses the quality of reperfusion (Schroder et al. 1994, Matetzky et al. 1999, Shah et al. 2000). ST-segment resolution ≥70% in the maximally involved lead 3 hours after the start of fibrinolysis predicts not only reperfusion but also the development of small infarcts (Schroder et al. 1994). In some patients, the elevation is not completely resolved and T-wave inversion fails to occur during the reperfusion phase of an AMI. The lack of ST-segment resolution has been acutely associated with failure to reperfuse and chronically with thinning of the left-ventricular wall caused by infarct expansion. Persistent ST-segment elevation after an AMI is indicative of dyskinetic wall motion (Arvan and Varat 1984). The most extreme manifestation of infarct expansion is the development of a ventricular aneurysm.

The first sign of reperfusion in patients with GI 3 is the reappearance of S waves. The decrease in the amplitude of the ST segment together with a reduction in the amplitude of the T waves is the most important sign of initial reperfusion. In GI 2 the most important sign of reperfusion is a progressive decrease in the size of T waves without any decrease in the ST segment (Sclarovsky 1999c).

2.7.3 Q wave

Classically the appearance of Q waves has been associated with irreversible myocardial necrosis. In animal studies the early appearance of Q waves may indicate reperfusion in the ischemic myocardium. Delayed appearance of Q waves is largely due to a lack of circulation in the infarcted area rather than to prolonged survival time (Blumenthal et al. 1975). In the early stages of STEMI the Q waves may not represent irreversible myocardial damage. This is supported by the findings of Raitt and associates (1995) showing that 53% of patients with STEMI admitted within 1 hour of onset of symptoms had abnormal Q waves on presentation, before the start of FT. The appearance of abnormal Q waves early in the course of acute MI did not lessen the benefit of reduced infarct size after FT. Others have also suggested that Q waves appearing within 6 hours of symptom onset may not represent irreversible damage and therefore do not preclude myocardial salvage by reperfusion therapy (Bar et al. 1987). The early appearance of a Q wave may reflect either irreversible damage or a large ischemic zone (Bar et al. 1987, Raitt et al. 1995). Q waves appearing early in the course of acute ischemia may be transient (Gross et al. 1964, Bateman et al. 1983, Rechavia et al. 1992).

2.7.4 ST-T patterns

The grade of coronary artery patency in the IRA may be predicted by the ST-T pattern. Early inversion of the T waves after fibrinolysis in patients with elevated ST segments indicates a better degree of reperfusion and ventricular function compared to cases with ST-segment elevation and positive T wave (Adler et al. 2000). Studies in which predischarge ECG and patency of IRA have been correlated have shown that the presence of a combination of negative T wave and isoelectric ST segment indicates good coronary flow. In contrast to this finding, the presence of a combination of positive T wave and elevated ST segment shows impaired coronary flow (Table 2 and Table 3).

Table 2. Sensitivity, specificity, positive predictive, negative predictive values and odds ratios of ECG findings for corrected TIMI frame count < 40 as a sign of normal epicardial blood flow (Atak et al. 2004).

ST-T pattern	Sensitivity %	Specificity %	PPV %	NPV %	OR (95% CI)
ST↔, T↓	51	85	89	42	5.77 (2.37-14.02)
ST↑, T↓	22	76	64	33	NS
ST↔, T↑	10	96	85	32	NS
ST↑, T↑	18	48	46	20	0.20 (0.096-0.43)

ST↔, isoelectric ST segment; ST↑, elevated ST segment; T↓, negative T wave; T↑, positive T wave; PPV, positive predictive value; NPV, negative predictive value; OR, odd ratio; CI, confidence interval; NS, nonsignificant

Table 3. Relationship between TIMI flow and the ST segment and T-wave deflections (Kusniec et al. 1997).

ST-T pattern	TIMI 0-1 %	TIMI 2 %	TIMI 3 %	p-value
ST↔, T↓	11	24	65	
ST↑, T↓	26	39	35	
ST↔, T↑	29	42	29	
ST↑, T↑	60	33	7	
				<0.001

ST↔, isoelectric ST segment; ST↑, elevated ST segment; T↓, negative T wave; T↑, positive T wave

2.7.5 Pre-infarction syndrome

Pre-infarction syndrome is the initial ECG manifestation of acute ischemia in STEMI. It occurs before the development of acute infarction. It is of the utmost importance to identify the distinct ECG characteristics at this window of opportunity before irreversible myocardial damage develops (Sclarovsky 1999b).

The ECG of the PIS is defined as positive, tall T waves and ST-segment elevation without new or old Q waves (Sclarovsky 1999b).

2.7.6 Evolving myocardial infarction

Myocardial damage occurring in the early evolving stage is usually responsive to treatment which either restores the myocardial oxygen supply or reduces the myocardial oxygen demand. However, in coronary events with more than 6 hours delay from symptom onset, therapeutic response is usually suboptimal (Tiefenbrunn and Sobel 1992). Crucial factors in determining the final infarct size are the duration of obstruction and its recurrence, the severity of obstruction, the degree of collateral function, and the myocardial oxygen demand at the time of occlusion. It is proposed to be useful to separate the causes of MI into 2 phases, the evolving and the convalescent phase (Pepine 1989). The former comprises the first 6 hours after the onset of symptoms suggestive of MI, while the convalescent phase comprises myocardial changes occurring after the first 6 hours and during the next few days.

Typically, during the evolution of AMI, pathological Q waves evolve and T-wave inversions develop. The T waves comprise two limbs, T1 and T2 (Kondo et al. 1996). The ECG can recognize three stages of effective reperfusion. Firstly, inversion of the T2 waves while T1 is still upright and elevated (biphasic T wave) along with the ST segment. Secondly, inversion of the two limbs of the T waves, with the peak inverted and beneath the isoelectric line (completely inverted T wave), while the ST segment still remains elevated above the isoelectric line. Thirdly, inversion of the T waves with an isoelectric ST segment (Sclarovsky 1999d). The ECG patterns of the EMI are shown in Table 4.

Table 4. The ECG patterns of evolving myocardial infarction. Modified from Sclarovsky (1999a).

Evolving MI with	**Q wave**	**ST segment**	**T wave**
No reperfusion	Yes	Elevated	Positive
Incomplete reperfusion	Yes or no	Elevated	Biphasic
Complete reperfusion	Yes or no	Isoelectric or mildly elevated	Completely inverted

MI, myocardial infarction

3. Anatomical interpretation of ECG in anterior STEMI

3.1 Principles

Only in the last few years, with the possibility of performing coronary angiography for large patient cohorts in the very early phase of an ACS with ST elevation, has it become possible to identify more exactly which coronary artery is occluded and at what level. The knowledge of coronary anatomy is a prerequisite for anatomical ECG interpretation.

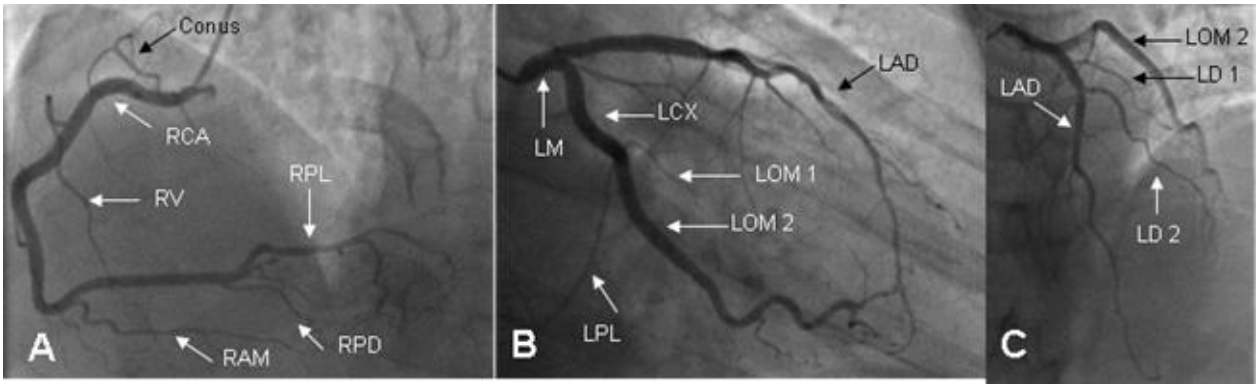


Figure 3. Coronary anatomy in right balanced dominance. A) Coronary angiography shows the right coronary artery (RCA) with the right posterolateral (RPL) and the right posterior descending (RPD) branch. B) The left main (LM) coronary artery divides into the left anterior descending (LAD) and the left circumflex (LCX) coronary arteries. C) The LAD wraps around the apex. The first left diagonal (LD1) side branch is small and the second left diagonal (LD2) side branch is medium-sized (≥1.5 mm vessel diameter).
RV, right ventricular; RAM, right acute marginal; LOM, left obtuse marginal; LPL, left posterolateral

The LAD generally subtends about 40% of the mass of the left ventricle (LV), with the LCX and the RCA supplying the remainder, to different degrees depending on vessel dominance (Kalbfleisch and Hort 1977)(Figure 3). The LAD supplies the anterior and anterolateral walls of the LV and two thirds of the interventricular septum. The lateral wall of the LV is variably supplied by the LCX, the LAD and a branch of the RCA. Isolated lateral wall infarctions usually involve occlusion of the LCX. More commonly, the lateral wall is involved with proximal occlusion of the LAD or a branch of the RCA. LAD occlusion proximal to the first left diagonal (LD) side branch results in more extensive myocardial necrosis than does distal occlusion.

ECG identification of anterior wall STEMI is made by recognizing ST-segment elevation in the standard precordial leads V_1 to V_4, usually caused by occlusion of the LAD (Blanke et al. 1984). AMI location is assigned based on the lead with maximal ST elevation identifying the core of ischemia. The frequency of ST elevation in patients with acute STEMI caused by LAD obstruction decreases in descending order: V_2, V_3, V_4, V_5, aVL, V_1 and V_6 (Aldrich et al. 1987). Extension to the lateral wall (anterolateral) results in additional ST-segment elevation located in leads I, aVL, V_5 or V_6 (Birnbaum et al. 1993c, Arbane and Goy 2000). Infrequently, obstruction of the RCA may cause ST elevation in leads V_1-V_4 especially with concomitant or isolated RVI (Geft et al. 1984, Coma-Canella et al. 1986, Eskola et al. 2007). ST-segment elevation in lead $V_1 \geq V_3$ and absence of progression of ST elevation from lead V_1 to V_3 on the ECG differentiates IRA-RCA from IRA-LAD in patients with combined anterior and inferior ST elevation (Sadanandan et al. 2003). Sometimes a proximal occlusion of a small, nondominant RCA produces an ECG pattern similar to that in occlusion of a side branch subtending the RV, ST elevation in leads V_4R and V_{1-3}, by reason of the absence of opponent posterior injury current (Eskola et al. 2004). These ECG changes may be misinterpreted as signs of infarction of the anterior wall, which emphasizes the importance of recording right-sided chest leads in patients with suspicion of ACS.

Some chronic ECG changes are confounders for anatomical ECG interpretation. Such conditions include LBBB, LVH, pathological Q wave and pacemaker ECG. Previous infarction or a history of previous cardiac surgery may also alter the ECG interpretation.

3.2 Site of lesion

The ECG recorded in the acute phase may enable identification of the site of coronary artery occlusion. By reason of the variability in the coronary anatomy, there may in some instances be more than one possible explanation for a specific ECG pattern. Moreover, since the size and exact location of the vascular bed supplied by the occluded artery varies considerably, occlusion in the same site of a coronary artery in different patients may result in a different size and location of the ischemic area at risk and hence different ECG changes. In addition, the presence of severe pre-existing narrowing in a non-culprit coronary artery may cause ischemia at a distance, which may alter the classic ECG picture. Many papers have been published assessing the correlation between various ECG patterns and the site of the culprit lesion. Usually they have

included only patients with single-vessel disease and a first MI, so that the applicability of these criteria to the general population, and especially to patients with prior STEMI or coronary artery bypass surgery is unclear.

Electrocardiographic identification of LAD occlusion is made on the basis of ST elevation in leads V_2-V_4 (Aldrich et al. 1987). Several ECG findings help to localize the occlusion site of the LAD with respect to its major branches (Table 5). Lead I faces the lateral region of the LV along with lead aVL, which faces the basal portion of the anterolateral free wall of the LV (Surawicz et al. 1978). ST elevation in these leads, accompanying ST elevation in leads V_5-V_6, has traditionally been defined as high lateral wall ischemia (Surawicz et al. 1978). In acute anterior STEMI, ST elevation in leads aVL and I signifies an LAD occlusion proximal to the first LD side branch (Arbane and Goy 2000, Birnbaum et al. 1993c). In contrast, ST depression in lead aVL during acute anterior STEMI is a marker of LAD occlusion distal to the first LD branch (Engelen et al. 1999). Isolated occlusion of the first LD branch may result in ST elevation in aVL (Sclarovsky et al. 1994).

ST depression in inferior leads II, III and aVF during acute anterior STEMI indicates injury to the basal anterolateral wall and does not signify inferior wall ischemia (Haraphongse et al. 1984, Fletcher et al. 1993, Chan et al. 2001). These reciprocal ST depressions in the inferior leads indicate LAD occlusion proximal to the first LD (Birnbaum et al. 1994, Engelen et al. 1999, Arbane and Goy 2000, Vasudevan et al. 2004). The magnitude of ST depression in inferior leads correlates better with that of ST elevation in leads I and aVL than with ST elevation in the precordial leads (Tamura et al. 1995). ST elevation in inferior leads signifies the presence of a large wrap around the apex LAD in cases with culprit lesion distal to the first LD (Martinez-Dolz et al. 2002).

Several ECG criteria have been reported to indicate LAD occlusion proximal to the first septal perforator branch. Some investigators have suggested ST elevation in lead V_1 and/or aVR as a marker of occlusion proximal to the first septal side branch (Engelen et al. 1999, Koju et al. 2003, Vasudevan et al. 2004), while other groups have found no association between ST elevation in lead V_1 and LAD occlusion proximal to the first septal branch (Ben-Gal et al. 1998, Czechowska et al. 2006). ST segment elevation in lead V_1 correlates with ST segment elevation in lead aVR (Czechowska et al. 2006). This fact may suggest that, although they lie on perpendicular planes, they are adjacent and represent ischemia of the same area. It has been suggested that because the right paraseptal area is supplied by the septal branches of the LAD, alone or together with the conal branch originating from the RCA, ST elevation in lead V_1 in

Table 5. Different concomitant ECG findings in anterior ST-elevation myocardial infarction (ST elevation in leads V_2-V_4) for localizing the occlusion site in the left anterior descending coronary artery with respect to its major branches.

ECG finding	Culprit lesion	Delay	n	Se %	Sp %	PPV %	NPV %
STE in leads I, aVL							
Engelen et al. 1999	Proximal to D1	< 14 d	100	58	81	57	57
Tamura et al. 1995	Proximal to S1 and D1	< 6 h	106	66	53	NA	NA
Arbane and Goy 2000	Proximal to D1	190 min	66	58	81	81	57
STE in lead aVR							
Koju et al. 2003	Proximal to S1 and/or D1	< 2 w	62	42	97	92	70
Engelen et al. 1999	Proximal to S1	< 14 d	100	43	95	86	70
Vasudevan et al. 2004	Proximal to S1	3 d	50	50	100	100	68
STD in leads II, III, aVF							
Birnbaum et al. 1994	Proximal to D1	11 d	122	32-43	90-96	NA	NA
Koju et al. 2003	Proximal to S1 and/or D1	< 2 w	62	85-88	67-78	66-73	87-89
Engelen et al. 1999	Proximal to D1	< 14 d	100	32-54	75-98	64-93	68-76
Vasudevan et al. 2004	Proximal to D1	< 3 d	50	82	90	89	80
Tamura et al. 1995	Proximal to S1 and D1	< 6 h	106	77	78	NA	NA
Arbane and Goy 2000	Proximal to D1	190 min	66	50-61	85-92	83-92	54-62

ECG, electrocardiogram; Delay, delay from ECG to coronary angiogram; n, number of patients; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; min, minutes; h, hours; d, days; w, weeks; NA, not available; S1, first septal branch; D1, first diagonal branch; STE, ST elevation; STD, ST depression

anterior STEMI suggests that the interventricular septum is not protected by a large conal branch of the RCA in addition to the septal branches of the LAD (Ben-Gal et al. 1997). In fact, the sensitivity of ST elevation >1 mm and >2 mm in lead V_1 for detecting a small conal branch is 81% and 97% with specificities of 71% and 26%, respectively (Ben-Gal et al. 1998). An ST-segment elevation ≤1 mm in lead V_1 has been reported to represent the presence of a large conal branch with a positive predictive value of 83%.

As the first septal branch carries the main blood supply to the distal part of the bundle of His and the proximal bundle branches, an anterior STEMI may generate a new complete right bundle branch block (RBBB). Complete RBBB has been reported as an ECG predictor of LAD occlusion proximal to the first septal branch (sensitivity 14% and specificity 100%) (Engelen et al. 1999). Ischemic RBBB is a rare finding in anterior STEMI in patients without ST elevation in lead V_1. Persistence of the conduction defect after reperfusion is associated with poor prognosis (Sclarovsky 1999e).

4. ECG in risk stratification

Final infarct size is determined by the location of infarction, the amount of myocardium perfused by the occluded artery (myocardium at risk), the severity of ischemia as graded by GI and the duration of the ischemia classified as PIS or EMI. Theoretically, knowing the variables involved in addition to the expected time to reperfusion may assist the clinician not only to make the diagnosis, but also to predict outcome and to choose the appropriate reperfusion therapy.

4.1 Prognostic value of infarct location

The infarct location of the STEMI is easily defined by the ECG (Table 1 [Page 23]). The location of AMI has significant influence on the patient's subsequent clinical course.

In the pre-reperfusion era, patients with inferior wall AMI had a significantly better prognosis and less myocardial damage than those with anterior wall AMI (Isomäki et al. 1969, Geltman et al. 1979). Patients with anterior MI had a higher in-hospital mortality (15.6 vs. 9.1%, p=0.001), and a higher prevalence of congestive heart failure (47.6 vs. 39.4%, p=0.007) and of

cardiogenic shock (12.6 vs. 8.7%, p=0.038) compared with inferior MI cases (Thanavaro et al. 1982).

In the FT era, the in-hospital mortality rate has been statistically significantly higher in anterior AMI (11.9 - 15.6%) than in inferior AMI (2.8 - 9.1%) and patients with anterior infarction had a larger infarct size, lower admission left ventricular ejection fraction and a higher incidence of heart failure compared with those with inferior infarction (Thanavaro et al. 1982, Stone et al. 1988). Also in long-term follow-up (mean 30.8 months), the total cumulative cardiac mortality has been higher in patients with anterior AMI compared with those with inferior infarction (27 vs. 11%, p<0.001, respectively) (Stone et al. 1988).

In the primary PCI era, among 2082 patients undergoing this procedure in the CADILLAC trial, those with anterior AMI had significantly higher mortality compared with non-anterior infarction both at 30 days (3.4 vs. 1.3%, p<0.001) and 1 year (6.5 vs. 2.9%, p<0.001) and had increased 1-year rates of re-infarction (3.6 vs. 1.7%, p=0.009) and higher rates of ischemic target vessel revascularization at 1 year (16.1 vs. 11.7%, p=0.006) (Kandzari et al. 2006).

Long-term (8 years) follow-up of the Zwolle trial showed no difference in mortality between streptokinase- and PCI-treated patients with non-anterior STEMI, but the streptokinase-treated FT group had a higher combined incidence of death and non-fatal re-infarction than the PCI group (39 vs. 24%, RR 2.1, CI 1.2-3.6). In univariate analysis in patients with anterior STEMI, mortality was higher in the FT (35 patients, 47%) than in the PCI group (19 patients, 25%) (RR 2.7, CI 1.4-5.5, p=0.004) (Henriques et al. 2006). The PRimary Angioplasty in patients transferred from General community hospitals to specialized PTCA Units with or without Emergency thrombolysis-2 (PRAGUE-2) trial enrolled 850 STEMI patients. At 5-year follow-up mortality among patients with anterior infarctions was 33 (streptokinase treated FT group) vs. 28% (primary PCI group), and for non-anterior infarct location 15 (FT) vs. 15% (PCI), differences not significant (Widimsky et al. 2007). In the DANAMI-2 trial, the combined incidence of total mortality, clinical re-infarction or disabling stroke rate in long-term follow-up (3 years) was lower in non-anterior STEMI treated with primary PCI compared with FT (alteplase) (HR 0.62, CI 0.43-0.88, p=0.007), but there was no difference in cases with anterior STEMI (HR 0.83, CI 0.63-1.07, p=0.15) (Busk et al. 2007).

A pooled analysis of 22 randomized clinical trials comparing primary PCI undertaken in order to prevent death with in-hospital FT in STEMI demonstrated that treatment with primary PCI was superior to FT in anterior but not in non-anterior infarctions regardless of presentation delay (Boersma and The Primary Coronary Angioplasty vs. Thrombolysis Group 2006).

In an everyday practice cohort a multivariable model showed that survival of patients with anterior STEMI treated with primary PCI compared with FT was associated with a reduced 30-day mortality rate (OR 0.3, CI 0.06–0.95, p=0.07) (Solodky et al. 2004).

4.2 Site of culprit lesion

In acute anterior STEMI, the myocardial area at risk is more extensive if the LAD occlusion is located proximal to the first side branch considered to be clinically significant compared to a distally located lesion. In general, compared to other vascular areas, AMI involving the LAD distribution is associated with reduced left ventricular function, less frequent collateral flow, impaired myocardial perfusion and decreased reperfusion success, all representing findings associated with reduced survival, and an increased incidence of major adverse cardiac events (Kandzari et al. 2006).

The observed prevalence of normal coronary angiography in patients presenting with acute chest pain and ST elevations is 2.6% and a normal angiogram during a biochemically confirmed infarction is extremely rare (0.7%) (Widimsky et al. 2006). Among patients with STEMI, the IRA is the LAD in 37-53%, the LCX in 12-18%, the RCA in 34-46% and a vein graft in 1-2% (Lundergan et al. 1998, van 't Hof et al. 1998b, Kandzari et al. 2006). In the LAD, the culprit lesion is located proximal to the first LD branch in 32-52 % (Engelen et al. 1999, Karha et al. 2003, Elsman et al. 2006).

Data from 2 large primary angioplasty trials demonstrated that death or repeat MI at 30 days was independently associated with LAD infarction (OR 1.89, CI 1.12-3.20) (Brener et al. 2000). In multivariable analysis in the CADILLAC trial, LAD infarction was a significant, independent predictor of 1-year mortality (OR 2.45, CI 1.25-4.80, p =0.009) (Kandzari et al. 2006).

Lesion locations and clinical outcomes were evaluated in 2 488 patients from the TIMI 4, 10A, 10B and 14 trials, all being studies comparing different fibrinolytic regimens. Proximal LAD culprit lesions were associated with an increased risk of in-hospital death or recurrent AMI compared with mid or distal LAD culprit lesions (12.0 vs. 7.2 vs. 0%, respectively, p=0.02). A quantitative analysis using digital planimetry demonstrated that the distance from the ostium to the LAD culprit lesion was shorter in patients who died or experienced a recurrent MI within 30 days (3.1 vs. 3.8 cm, p=0.01). After adjustment for age, gender, heart rate on admission and

angiographic TIMI grade 3 flow, the distance from the ostium to the LAD culprit lesion was associated with 30-day death or recurrent MI (OR 0.79 reduction per centimeter increase in distance down the artery, p=0.01) (Karha et al. 2003).

In patients with acute STEMI treated with primary PCI soon after onset of symptoms, proximal LAD culprit lesions are associated with higher 30-day and 3-year mortality compared with distal LAD culprit lesions (5 vs. 1%, p=0.002 and 10 vs. 3%, p<0.001, respectively). After adjustment for age, gender, diabetes mellitus, ischemic time and multivessel disease, the relative risk of 3-year mortality for proximal vs. distal LAD culprit lesions was 4.04 (CI 1.95-8.38). No difference was seen in adjusted 3-year mortality between patients with distal LAD culprit lesions and non-LAD culprit lesions (p=0.145) (Elsman et al. 2006). Comparing outcomes among patients with LAD infarction relative to location of the culprit lesion, mortality tended to be higher among those with an ostial/proximal location vs. a mid/distal location at 30 days (8.9 vs. 3.3%, p=0.053), although these differences did not vary significantly at 1 year (8.9 vs. 6.6%, p=0.52) (Kandzari et al. 2006).

There are no studies in the English-language literature concerning the significance for prognosis or therapeutic approach selected of ECG-based determination of the site of culprit lesions in patients with anterior STEMI.

4.3 Sum of ST deviation

Several studies have sought to estimate the ischemic area at risk or final infarct size on the basis of the admission ECG. In these studies, either the number of leads with ST deviation (elevation and/or depression) or the absolute amplitude of ST deviation was used. The sum of the absolute ST-segment deviation (both ST elevation and ST depression) has been reported as the independent predictor of poorer outcome after AMI (Willems et al. 1990, Hathaway et al. 1998); however, contradictory results have also been published. According to other studies, estimates of the myocardial area at risk based on these ECG variables are of minimal clinical value in the individual patient (Clements et al. 1991, Christian et al. 1995).

In the DANAMI-2 trial sub-study, 1420 patients had baseline ST-segment deviation measurements and were assigned to quartiles according to the sum ST-segment deviation (ΣST): first 0 to 6.5, second 7.0 to 9.5, third 10.0 to 14.5 and fourth 15.0 to 70.5 mm (Sejersten et al. 2006b). The composite and component end-point rates at 30 days were determined for each

quartile. The composite end point occurred more often with increasing ΣST (p=0.05). With regard to component end points, only mortality increased proportionately with increasing ΣST (p=0.03), whereas re-infarction and stroke rates were independent of the initial magnitude of ΣST. In multivariable analysis, ΣST was an independent predictor of mortality. The occurrence of death within 30 days increased with ΣST for patients with anterior AMI location (4.3% in the first, 5.2% in the second, 8.2% in the third and 10.2% in the fourth quartile, p=0.025), but not with inferior AMI location.

The lower composite end point rate of primary PCI compared with FT was observed only in the fourth ΣST quartile (Sejersten et al. 2006b). Absolute re-infarction rates were significantly lower in patients treated with primary PCI than with FT regardless of ΣST (4.2% in first, p=0.03; 5.4% in second, p=0.004; 4.6% in third, p=0.03; and 5.0% in fourth quartile, p=0.03), whereas mortality and stroke rates were similar in each quartile.

4.4 Grade of ischemia

In patients with STEMI treated with FT or primary PCI, the finding of GI 3 on the presenting ECG is a very strong independent predictor of failure to achieve myocardial perfusion as assessed both electocardiographically and angiographically (Buber et al. 2005, Wolak et al. 2007). This association may explain the larger infarcts, less viability in the infarcted zone, less benefit from FT and poorer prognosis associated with GI 3 compared with GI 2 found in several studies (Birnbaum et al. 1996b, Birnbaum et al. 2002, Sucu et al. 2004, Sejersten et al. 2006a). It would appear that the difference in infarct size between GI 2 and GI 3 is not explained by larger area at risk (Birnbaum et al. 2002).

Distorsion of the terminal portion of the QRS complex on the admission ECG is an independent predictor for adverse prognosis. In-hospital mortality has been 0% in GI 1 (Birnbaum et al. 1993a, Garcia-Rubira et al. 1995), while in GI 2 in-hospital mortality has varied from 3 to 7.9%, and in GI 3 from 6 to 29% (Birnbaum et al. 1993a, Garcia-Rubira et al. 1995, Birnbaum et al. 1996a). The difference in in-hospital mortality between GI 2 and GI 3 has been similar in anterior and inferior AMI (Garcia-Rubira et al. 1995). Long-term prognosis was studied in the TIMI 4 trial and no difference was found among patients with non-anterior AMI, while in patients with anterior AMI one-year mortality was higher in GI 3 than in GI 2 (18 vs. 6%, p=0.03) (Birnbaum et al. 1996b).

In the GUSTO-I trial, in-hospital mortality among patients treated within 2 hours from onset of symptoms was comparable between those with GI 2 and GI 3 (4.2 vs. 5.3%, respectively). However, among patients treated with FT 2 to 6 hours after onset of symptoms, mortality increased to 7.4% among those with GI 3, whereas it did not change among those with GI 2 (3.6 %, p=0.0005) (Birnbaum et al. 1996a). Accordingly, it is conceivable that in patients with GI 3 the beneficial effect of salvaging the myocardium with FT is lost after 2 hours because of a more rapid rate of progression of the wavefront of necrosis. Pretreatment and predischarge technetium-99m sestamibi single-photon emission computed tomography imaging in patients undergoing FT and primary PCI has shown that salvage decreases as time from onset of symptoms to treatment increases only in GI 3 patients; in GI 2 patients the association between salvage and time was not significant (Birnbaum et al. 2002, Billgren et al. 2005).

In the GUSTO IIb trial in-hospital mortality was similar in GI 2 and GI 3 among patients randomized to primary PCI and FT (Birnbaum et al. 2001). In the DANAMI 2 trial, 30-day mortality was higher for GI 3 than for GI 2 (9.7 vs. 4.8%, p<0.001) and doubled for patients treated late (>3 hours after symptom onset) compared to patients treated early (GI 2: 6.0 vs. 3.3%, p=0.01; GI 3: 12.5 vs. 4.7%, p=0.05, respectively) (Sejersten et al. 2006a). Overall mortality did not differ between FT and primary PCI, although a 5.5% absolute mortality reduction trend was seen in GI 3 treated early with primary PCI (6.9 vs. 1.4%, p=0.10, respectively). The re-infarction rate was lower among patients treated with primary PCI than with FT in both patients with GI 2 (1.6 vs. 7.2%, p<0.001, respectively) and with GI 3 (0 vs. 7.9%, p<0.001, respectively).

4.5 Pre-infarction syndrome and evolving myocardial infarction

There are no reports in the English-language literature concerning the impact of PIS and EMI ECG patterns on prognosis or therapeutic approach adopted in patients with STEMI.

5. Computerized ECG analysis in STEMI

In the 1950s, the first step toward computerized ECG analysis was taken with the successful development of the analog to digital converter. Electrical ECG signals could now be transformed

into digital information which could then be processed by computer. The first published reports on computerized ECG analysis emerged in the early 1960s (Pipberger et al. 1961, Caceres et al. 1962). Despite the significant limitations of the initial systems, it was early recognized that progressive development of computerized ECG analysis would have much to contribute in future years (Burchell and Reed 1976). The first commercial 12-lead ECG analysis program was made available by Marquette Electronics in the early 1980s, closely followed by Siemens-Elema. Nowadays it is estimated that over 100 million ECGs are analyzed by computer annually in the United States, with a similar number in Europe and in the rest of the world (Hongo and Goldschlager 2006).

5.1 Accuracy of computer-interpreted ECG

In a large-sized trial with more than 5000 ECGs, the overall sensitivity of computer interpretation was 90%, specificity 90%, PPV 87% and NPV 92% as compared to manual analysis by expert readers. Sensitivity and specificity were lowest for the category of ST-T wave changes (83 and 84%, respectively) (Thomson et al. 1989). Guglin and Thatai (2006) found the overall error rate of computerized ECG analysis to be 15.9% for all abnormal ECGs. The most frequent errors in computer ECG interpretation were related to arrhythmias, conduction disorders and pacemakers.

The Marquette 12SL ECG analysis program measures ST voltages at the J point, the STM point (J + $\frac{1}{16}$ average R-R interval) and the STE point (J + $\frac{1}{8}$ average R-R interval). The best indicator for new anterior STEMI, in descending order of sensitivity and specificity, is the STE point (79 and 93%, respectively) followed by the STM (75 and 91%, respectively) and STJ points (72 and 89%, respectively) (Elko and Rowlandson 1992).

In the detection of acute myocardial injury by ST segment assessment, computer ECG analysis has been found to have lower sensitivity (52 vs. 66%, respectively, $p<0.001$), but higher specificity (98 vs. 95%, respectively, $p<0.001$) compared with expert readers (Kudenchuk et al. 1991). The correct diagnosis of acute epicardial injury was significantly affected by the location of the ST segment elevation. The sensitivity of the computer analysis was 56% in cases with anterior ST elevation compared with 87% in those with inferior ST elevation ($p<0.001$) (Kudenchuk et al. 1991). It has been reported that the median sensitivity of the nine different

computer programs is significantly lower than that of cardiologists in diagnosing anterior (77 vs. 85%, p< 0.001) and inferior MI (59 vs. 72%, p<0.0001) (Willems et al. 1991).

5.2 Value of selecting patients for reperfusion therapy

Some data suggest that strict reliance on manually measured ECG criteria alone may lead to inappropriate overuse of FT. Agreement for suspected AMI tended to be better when the subjective opinion that ECG changes observed represent acute transmural injury (interpretive) was added to measurable ST elevation criteria (Massel et al. 2000). The study in question also showed that although the Marquette 12SL system had excellent specificity (100%), it had poor sensitivity (62%) for the diagnosis of fibrinolysis-eligible AMI. Reliance on computerized ECG interpretation could result in inappropriate underuse of FT in situations in which qualifying ECG criteria are actually met.

6. Transmission of ECG data

Time to reperfusion is critical for outcome in patients with STEMI. It has been demonstrated that transmission of the ECG from the prehospital interaction site to hospital emergency departments can reduce the time to reperfusion therapy (Weaver et al. 1993). However, triage delays ensue when attending cardiologists are not alerted or are located distant to the ECG receiving station. The technology allows transmission to a hand-held device carried by the attending cardiologist for immediate ECG evaluation irrespective of physical location. Although prehospital transmission of the ECG to special receiving stations has been technically possible since 1987 (Grim et al. 1987), transmission to hand-held pocket computers or mobile phones has only recently become an option.

There is a high degree of diagnostic concordance among cardiologists viewing either traditional paper ECGs or cellular telephone liquid crystal display screen ECGs (Leibrandt et al. 2000). ECG transmission problems such as failure of cellular connection between receiving station and mobile telephone, modem and network errors, defect in the mobile telephone, delayed visualization of ECG on the mobile phone or ambulance location preventing ECG transmission have been demonstrated in as many as 18% of transmissions (Sejersten et al. 2008).

Nonetheless, in some clinical trials, the final success rate of ECG transmission from the field has been consistently high, ranging around 93% (Clemmensen et al. 2005, Sejersten et al. 2008). A recent study showed that prehospital 12-lead ECG transmission directly to a cardiologist's mobile telephone with immediate triage and referral of patients with STEMI directly to a catheterization suite, bypassing local hospitals, significantly reduced door-to-PCI time (Sejersten et al. 2008).

It might be envisaged that cardiologists would be equipped with a device capable of receiving and displaying ECGs. Patients diagnosed by the on-call cardiologist as having a STEMI would then bypass the emergency room and go directly to the catheterization laboratory. Immediate access of the diagnostic ECG to a health professional with decision competence to activate the catheterization suite is essential to reduce the time to treatment. The ECG from the acute phase should be compared with previous recordings, if available. Regional logistic systems with immediate access to digitally stored ECGs have been developed. From a technical perspective, reference ECGs could be made available anywhere and anytime at the very onset of an acute coronary event through internet-based telemedicine.

7. Reperfusion therapy in STEMI

An occlusive coronary arterial thrombus at the site of a ruptured plaque is the primary mechanism leading to an MI (Davies et al. 1976, DeWood et al. 1980, DeWood et al. 1983, Mizuno et al. 1992). In patients with STEMI, the primary objective of therapy is to restore blood flow in the IRA. The aim of reperfusion therapy in STEMI is to reduce mortality and morbidity. Reperfusion can be obtained pharmacologically (FT) or mechanically (PCI).

The management of patients with STEMI has evolved considerably during the last few decades. The first report of successful reperfusion of occluded coronary arteries with FT in patients with STEMI was made 29 years ago (Rentrop et al. 1979). Direct coronary angioplasty as the primary reperfusion therapy for STEMI was first described by Meyer and Hartzler in the early 1980s (Meyer et al. 1982, Hartzler et al. 1983). The first prospective randomized report on the feasibility and safety of primary PCI vs. FT was published more than 20 years ago (O'Neill et al. 1986). During the past decade, primary PCI has gradually emerged as the preferred treatment strategy for AMI with ST-segment elevation (Weaver et al. 1997, Keeley et al. 2003, Van de Werf et al. 2003).

7.1 Fibrinolytic therapy

In comparison with conservative management (medical treatment without reperfusion therapy), FT leads to improved left ventricular systolic function and survival in patients with MI associated with either ST-segment elevation or LBBB. In a pooled analysis of nine large trials, the rate of death at 35 days was 9.6% among patients receiving FT as compared with 11.5% among control patients. FT was associated with an excess of deaths during days 0-1 (especially among patients presenting more than 12 hours after symptom onset and in the elderly), but this was out-weighed by a much larger benefit during days 2-35 (Fibrinolytic therapy trialists' (FTT) collaborative group 1994). Intravenous infusion of streptokinase within 6 hours after symptom onset reduced 30-day total vascular mortality by 25%, but at a cost of 2-3 strokes per 100 patients treated and of 3 severe bleedings requiring transfusion per 1000 patients treated.

Combined treatment including both FT and aspirin has synergistic effects and prevents 52 vascular deaths per 1000 patients treated and significantly reduces the risk of re-infarction (ISIS-2 (second international study of infarct survival) collaborative group 1988). The initial benefit of streptokinase treatment in terms of mortality has been maintained at 10-year follow-up with an absolute benefit of 19 (95% CI 1-37) lives saved per 1000 patients treated (Franzosi et al. 1998). The use of recombinant tissue plasminogen activator (rt-PA) instead of streptokinase, provides a survival benefit representing a 14% reduction (CI 5.9-21.3) in mortality at 30-day follow-up ($p=0.001$). Although rt-PA plus heparin instead of streptokinase prevents a further 10 deaths, it causes 2 more strokes per 1000 patients treated (The GUSTO investigators 1993).

In the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis in Myocardial Infarction Study 25 (ExTRACT-TIMI 25) trial, 20 479 patients undergoing fibrinolysis for STEMI with a fibrin-specific agent (n=16 283) or streptokinase (n=4139) were randomized to enoxaparin throughout their hospitalization stay or to unfractionated heparin (UFH) for at least 48 h. In the multivariable analysis, including components of the TIMI risk score, the primary end-point of death or nonfatal recurrent MI through 30 days occurred in 12.0% of patients in the UFH and 9.8% in the enoxaparin groups when treated with fibrin-specific lytics (odds ratio (OR) 0.78, CI 0.70-0.87, $p<0.001$) and 11.8 vs. 10.2%, respectively, when treated with streptokinase (OR 0.83, CI 0.66-1.04, $p=0.10$). Major bleeding rates including intracranial hemorrhage (ICH) within the fibrin-specific cohort were 1.2 and 2.0% in the UFH and enoxaparin groups, respectively ($p<0.001$) and 2.0% in UFH and 2.4% in enoxaparin patients in the streptokinase cohort ($p=0.16$). Death, nonfatal MI or major bleeding

was significantly reduced with enoxaparin in the fibrin-specific cohort (OR 0.82, CI 0.74-0.91, p<0.001) and favoured enoxaparin in the streptokinase cohort (OR 0.89, CI 0.72-1.10, p=0.29). According to the ExTRACT-TIMI 25-trial, anticoagulant therapy with a strategy of enoxaparin throughout the index hospitalization is superior to the standard strategy of 2 days of UFH in STEMI patients undergoing pharmacological reperfusion (Giraldez et al. 2007).

7.1.1 Limitations of fibrinolytic therapy

Despite several advantages, including development of fibrin-specific lytics and bolus-administered agents, FT is clearly imperfect. Full antegrade perfusion (TIMI grade 3 flow) is achieved in only 30 to 55% of patients (The GUSTO angiographic investigators 1993, Cannon et al. 1994). The benefits of fibrinolysis are compromised when reocclusion of successfully re-perfused infarct arteries occurs. After initially successful fibrinolysis, 5% (control coronary angiography at 180 minutes after the initiation of fibrinolytic therapy) to 12% (control coronary angiography at 7 days) of patients experience reocclusion of the culprit coronary artery (Ohman et al. 1990, The GUSTO angiographic investigators 1993). When this occurs, reocclusion is associated with recurrent infarction and an increased risk of mortality and morbidity. Patients suffering reocclusion have a more complicated hospital course and higher in-hospital mortality rates than those without reocclusion (11.0 vs. 4.5%, respectively, p=0.01) (Ohman et al. 1990). At 3 months after successful fibrinolysis, the reocclusion rate has been 25% among patients treated with aspirin, 30% with coumadin and 32% with placebo as adjunctive medication after FT (p=not significant) (Meijer et al. 1993). In the same study, re-infarction was seen in 3% of patients on aspirin, in 8% on coumadin and in 11% on placebo (aspirin vs. placebo, p<0.025; other comparison, p=not significant). A study by Mueller and associates (1995) showed that during a 3-year follow-up, 349 out of 3 339 patients (10%) treated with rt-PA sustained a nonfatal re-infarction. The cumulative 3-year death rate was 14.1% in patients with a nonfatal re-infarction compared with 7.9% (p<0.01) in a matched control group.

The most feared complication of FT is ICH, since fatality rates can rise to 66% in a period of 18 months (De Jaegere et al. 1992). The incidence of ICH with FT remains at approximately 0.53 to 1.0% (Carlson et al. 1988, De Jaegere et al. 1992, Kase et al. 1992). Nonhemorrhagic stroke also remains a major cause of death and disability in this population. In a large trial (n=41 021) 1.4% of STEMI patients had a stroke. Primary ICH rates ranged from 0.46 to 0.88% between 4 fibrinolytic strategies. Of all strokes, 41% were fatal, 31% were disabling and 24%

nondisabling. Patients with primary ICH had the poorest prognosis: 60% of them died and another 25% were disabled. Patients who had nonhemorrhagic strokes had a better prognosis, with 17% deceased and 40% disabled. Patients with moderate or severe residual deficits showed significantly diminished quality of life (Gore et al. 1995). Increased rates of ICH have been noted in patients with low body weight and patients aged >75 years (Gore et al. 1995, Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators 2001, Topol and GUSTO V Investigators 2001, Ahmed et al. 2006).

7.1.2 Pre-hospital fibrinolysis

When FT is administered on-site by the first qualified person to see the patient, the term pre-hospital fibrinolysis is used. The extent of myocardial damage occurring during AMI is time-dependent and there is abundant evidence from clinical trials that mortality reduction is greatest in patients treated early with fibrinolytic agents. Pre-hospital fibrinolysis can thus clearly reduce mortality. In the randomized Grampian Region Early Anistreplase Trial (GREAT), fibrinolysis was given intravenously either before hospital admission or in the hospital, at a median of 105 and 240 min, respectively, after onset of symptoms (Rawles 1997). The 5-year results showed that 41 (25%) out of 163 patients had died in the prehospital treatment group compared with 53 (36%) out of 148 in the hospital treatment group (log-rank test, $p<0.025$). Delaying fibrinolytic treatment by 1 hour appears to increase the death hazard ratio by 20%, equivalent to a loss of 43/1000 lives within the next 5 years (CI 7 to 88, $p=0.012$). Delaying fibrinolytic treatment by 30 minutes, again, reduces the average expectation of life by approximately 1 year.

7.1.3 Contraindication to fibrinolysis

Absolute contraindications to FT are hemorrhagic stroke or stroke of unknown origin at any time, ischemic stroke in the preceding 6 months, central nervous system damage or neoplasms, recent major trauma/surgery/head injury within the preceding 3 weeks, gastro-intestinal bleeding within the last month, known bleeding disorder and aortic dissection. Relative contraindications to FT are transient ischemic attack in the preceding 6 months, oral anticoagulant therapy, pregnancy or within 1 week post partum, non-compressible punctures, traumatic resuscitation,

refractory hypertension (systolic blood pressure >180 mmHg), advanced liver disease, infective endocarditis and active peptic ulcer. (Van de Werf et al. 2003)

7.2 Primary PCI

The role of PCI during the early hours of STEMI can be divided into primary PCI, PCI combined with pharmacological reperfusion therapy and rescue PCI after failed pharmacological reperfusion. The last two issues are not discussed in this context. Primary PCI is defined as angioplasty and/or stenting without prior or concomitant FT in patients with acute STEMI (Van de Werf et al. 2003). Technically, the current method of primary PCI is to cross the occlusion with a balloon catheter, which, after a brief period of inflation, re-establishes blood flow. Subsequently, one or more stents are placed to provide stable revascularization.

7.2.1 Benefits of primary PCI

Immediate information on the coronary anatomy facilitates accurate risk stratification of a STEMI patient and allows the most appropriate individual treatment strategy to be implemented. Primary PCI can be performed with success in a large majority of patients with a contraindication to FT (Brodie et al. 1991, Mossard et al. 1991). Primary PCI is effective in securing and maintaining coronary artery patency and avoids some of the bleeding risk of fibrinolysis. In a report on 4366 primary PCIs performed at 40 sites in the United States between 1990 and 1994, the success rate (the proportion of patients with a patent IRA at the end of the procedure) was 91.5% (Grassman et al. 1997). However, lower procedural success has been reported in elderly (80%) compared to younger (<75 years old) patients (91%), (p=0.031) (Wenaweser et al. 2007).

7.2.2 Limitations of PCI

Complications occasionally occur as a result of primary PCI. Local vascular complications include bleeding, hematomas, pseudoaneurysms and arteriovenous fistulae at the access-site. Access-site hematoma in the setting of PCI is the most frequent periprocedural complication (2-

10%) (Dangas et al. 2001, Piper et al. 2003). According to Yatskar and associates (2007), the incidence of access-site hematoma requiring transfusion (HRT) was 1.8% and femoral access was common. Independent predictors of HRT include age, female sex, treatment with IIb/IIIa inhibitors or fibrinolytic agents, emergency priority, MI, shock, and concomitant renal, cerebrovascular, peripheral vascular and pulmonary disease (Piper et al. 2003, Yatskar et al. 2007). Lesions encountered in patients developing HRT are more often calcified, thrombotic, located in an ostial location, or class B2 or C (Piper et al. 2003, Yatskar et al. 2007). HRT is independently associated with in-hospital mortality (OR 3.59, CI 1.66-7.77, p=0.001) and 1-year death (OR 1.65, CI 1.01-2.70, p=0.048) (Yatskar et al. 2007). The use of the radial approach leads to fewer vascular complications than the femoral approach. The radial approach fails in 8%. Time from arrival in the catheterization laboratory to the first balloon inflation was longer in patients with a failed radial approach compared to the femoral (61 ± 11 min vs. 39 ± 19 min, respectively), but similar with a successful radial approach (Ziakas et al. 2007).

The successful restoration of epicardial coronary artery patency, however, does not necessarily translate into improved tissue perfusion. When a coronary artery is occluded, detrimental changes occur in the cardiac capillaries and arterioles. After relief of the occlusion, blood flow to the ischemic tissue may still be impeded, a phenomenon known as no reflow. Failure to restore myocardial perfusion may be caused by any of three main pathogenetic components alone or in combination: distal atherothrombotic embolization, ischemia-reperfusion injury and susceptibility of coronary microcirculation to injury (Ito H 2006). Myocardial perfusion, as evidenced by normal contrast opacification of the myocardial bed subtended by the infarct artery (myocardial blush), was normal in only 29.4% of patients with TIMI flow grade 3 following PCI, and in no patient with TIMI flow grade 0 to 2. Within a cohort of patients with restored TIMI flow grade 3, survival was strongly dependent on the myocardial perfusion grade; the one-year cumulative mortality was 6.8% with normal myocardial blush, 13.2% with reduced myocardial blush and 18.3% in patients with absent myocardial blush (p=0.004) (Stone et al. 2002). When successful reperfusion was defined as postprocedural TIMI flow grade 3 with myocardial blush grades 2 to 3, unsuccessful myocardial reperfusion was observed in 358 out of 1548 consecutive patients (23.1%) with STEMI and was associated with larger infarct size and lower ejection fraction (De Luca et al. 2005). In multivariable analysis, including clinical and angiographic variables, unsuccessful reperfusion was an independent predictor of 1-year mortality (RR 3.11, CI 1.99-4.87, p<0.0001) (De Luca et al. 2005).

In some patients, embolization of microscopic debris with balloon inflation or stent deployment induces microvascular obstruction and diminishes myocardial reperfusion. In such patients, the magnitude of the ST-segment elevation is not diminished, even though antegrade flow in the epicardial artery is restored (Matetzky et al. 1999, Prasad et al. 2005). Among such patients, survival is correspondingly reduced (Sorajja et al. 2005). Manual thrombus aspiration is a promising and feasible means in a large majority of patients to reduce distal embolization. As compared with balloon angioplasty as an initial step in primary PCI, aspiration before stenting results in improved myocardial reperfusion, documented by a clear improvement in the myocardial blush grade, increased resolution of ST-segment elevation and reduced residual ST-segment deviation (Svilaas et al. 2008). Compared with conventional PCI, thrombus aspiration before stenting of the IRA seems to improve the 1-year clinical outcome after primary PCI for STEMI. Cardiac death at 1 year was 3.6% (19 out of 535 patients) in the thrombus aspiration group and 6.7% (36 out of 536) in the conventional PCI group (HR 1.93, 95% CI 1.11-3.37, p=0.020). 1-year cardiac death or non-fatal re-infarction occurred in 5.6% (30 out of 535) of patients in the thrombus aspiration group and 9.9% (53 out of 536) of patients in the conventional PCI group (HR 1.81, 95% CI 1.16-2.84, p=0.009) (Vlaar et al. 2008).

Although rare, cerebrovascular accidents after PCI in general are associated with high rates of in-hospital death and acute renal failure, often requiring dialysis. When an untoward cerebrovascular event was defined as a composite of transient ischemic attack (TIA) and stroke, such a contretemps occurred in 92 out of 20 679 patients (0.30% of procedures). Of these, TIA occurred in 13 patients (0.04%) and stroke in 79 (0.26%) (Dukkipati et al. 2004).

Severe nephropathy after PCI (caused, at least in part, by radiographic contrast material) occurs in up to 2% of patients in unselected materials (Bartholomew et al. 2004). It occurs most often among those with cardiogenic shock (Hochman et al. 1999) or underlying renal insufficiency (Sadeghi et al. 2003) and in subjects of advanced age (DeGeare et al. 2000). Anaphylactic reactions to radiographic contrast material are very rare. The incidence of contrast media complications occurring in the catheterization laboratory is 0.23%, with 1 death per 55 000 angiograms (Johnson et al. 1989, Lozner et al. 1989).

Ventricular tachycardia or fibrillation has been reported in 133 out of 3065 patients (4.3%) undergoing primary PCI. These arrhythmias did not influence PCI success or in-hospital or 1-year outcomes (Mehta et al. 2004). A 4.3% rate of emergency surgery has been reported in cases of primary PCI. Unsuccessful angioplasty is one predictor of the need for emergency surgery (Grassman et al. 1997).

7.3 Studies comparing primary PCI and fibrinolytic therapy

A meta-analysis of 23 randomized trials comparing primary PCI with FT for the treatment of acute STEMI reported an overall reduction in short-term (4-6 weeks) deaths (5 vs. 7%, p=0.0003), non-fatal re-infarctions (3 vs. 7%, p<0.0001) and strokes (1 vs. 2%, p=0.0004) (Keeley et al. 2003). Major bleeding (defined as ICH or bleeding which caused hemodynamic compromise or necessitated blood transfusion, or both) was the only end-point for which individuals were at greater risk when treated with primary PCI rather than fibrinolysis (7 vs. 5%, OR 1.3, CI 1.02-1.65, p=0.032).

The early benefit from the primary PCI strategy as against FT is sustained during long-term follow-up. The Danish multicentre randomized study of FT vs. primary angioplasty in AMI, DANAMI-2, is the largest trial to compare on-site fibrinolysis with inter-hospital transfer for primary PCI. The absolute reduction in the composite end-point (total mortality, clinical re-infarction or disabling stroke) rate was 5.7% at 30 days (Andersen et al. 2003b) and 5.6% after 3 years in favor of primary PCI (Busk et al. 2007). The number needed to treat to avoid one combined end-point within 3 years was 18 for all hospitals and 15 for referral hospitals. For patients receiving on-site fibrinolysis compared with primary PCI, death occurred in 15.0 vs. 13.7% (p=0.46), clinical re-infarction in 12.3 vs. 8.3% (p=0.007), disabling stroke in 4.1 vs. 3.0% (p=0.23); angioplasty had been performed in 34 vs. 16% (p<0.001) and coronary artery bypass surgery in 12 vs. 9% (p=0.07) at 3-year follow-up (Busk et al. 2007). Long-term results obtained by a retrospective method have been reported from the PRAGUE-2 randomized trial, in which inter-hospital transfer for angioplasty was compared to on-site treatment with streptokinase (Widimsky et al. 2007). At 5-year follow-up, the cumulative incidence of composite end-point (death from any cause or recurrent MI or stroke or revascularization) was 53% in FT patients compared with 40% in primary PCI patients (HR 1.8, CI 1.38-2.33, p<0.001). The corresponding cumulative incidence of death from any cause was 23 and 19% (HR 1.34, CI 0.99-1.82, p=0.06), recurrent infarction 19 and 12% (HR 1.72, CI 1.15-2.58, p=0.009), stroke 8 and 8% (HR 1.65, CI 0.84-2.23, p=0.18), (re-)PCI 38 and 22% (HR 2.12, CI 1.51-2.99, p<0.001), coronary artery bypass surgery 13 and 12% (HR 1.13, CI 0.75-1.71, p=0.56), respectively. A sustained benefit from primary PCI during long-term follow-up has also been reported from the smaller but pioneering Zwolle and PAMI trials (Nunn et al. 1999, Zijlstra et al. 1999).

The Comparison of Angioplasty and Prehospital Thrombolysis In acute Myocardial infarction (CAPTIM) trial was set up to compare prehospital fibrinolysis and primary PCI in patients with STEMI (Bonnefoy et al. 2002). The rate of primary end-point (a composite of death, non-fatal re-infarction and non-fatal disabling stroke within 30 days) was 8.2% in the pre-hospital fibrinolysis group and 6.2% in the primary PCI group (p=0.29). Mortality, re-infarction or disabling stroke rates did not differ significantly between the fibrinolysis and angioplasty groups. In the fibrinolysis group, 106 (26%) patients had rescue PCI immediately after fibrinolysis, angiography was perfomed (not scheduled by protocol) up to day 30 in 358 (85.4%) and angioplasty in 295 (70.4%) patients.

A prospective observational cohort study of 26 205 consecutive STEMI patients in the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) who received reperfusion therapy within 15 hours from symptom onset included more than 95% of all Swedish patients of all ages treated in a coronary intensive care unit between 1999 and 2004 (Stenestrand et al. 2006). After adjusting for younger age and less comorbidity, primary PCI was associated with lower mortality than prehospital fibrinolysis at 30 days (4.9 vs. 7.6%, HR 0.70, CI 0.58-0.85) and 1 year (7.6 vs. 10.3%, HR 0.81, CI 0.69-0.94). Beyond 2 hours' treatment delay, the observed mortality reductions with prehospital fibrinolysis tended to decrease while the benefits with primary PCI seemed to remain regardless of time delay. Primary PCI was also associated with shorter hospital stay.

The impact of general high-risk predictors for adverse outcome is similar in primary PCI as in other STEMI treatment strategies. Among patients with cardiogenic shock, the overall mortality at 6 months was 50.3% in the emergency revascularization (PCI [54.6%] or coronary artery bypass surgery [37.5%]) groups and 63.1% in patients with medical therapy only (p=0.027) . In the Second National Registry of Myocardial Infarction, patients with congestive heart failure had a 33% relative risk reduction with primary PCI compared with a 9% relative risk reduction with FT (Wu et al. 2002).

7.3.1 Time delay

Recent evidence from several large trials suggests that the maximum benefits of either reperfusion strategy may be attained at different time-points after symptom onset. The CAPTIM trial (n=834) showed that patients randomized <2 hours after symptom onset (n=460) had a strong trend toward lower 30-day mortality with prehospital FT compared with those

randomized to primary PCI (2.2 vs. 5.7%, p=0.058), whereas mortality was similar in patients randomized ≥2 hours (5.9 vs. 3.7%, p=0.47) from symptom onset (Steg et al. 2003). Among patients randomized in the first 2 hours, cardiogenic shock was less frequent with FT than with primary PCI (1.3 vs. 5.3%, p=0.032), whereas these rates were similar in patients randomized later. The PRAGUE-2 study observed no difference in 30-day mortality between FT and primary PCI for patients randomized within 3 hours of symptom onset (n=551) (Widimsky et al. 2003). Among 299 patients randomized >3 hours after the onset of symptoms, mortality of the FT group reached 15.3% compared to 6% in the primary PCI group (p<0.02). The early benefit from primary PCI strategy as against FT was sustained during the 5 years' follow-up. Patients randomized within 3 hours had a long-term mortality of 19.8% (FT) and 20.9% (primary PCI, p=0.11). Long-term mortality among patients presenting late (≥3 hours after symptom onset) was 32.1% (FT) and 20.7% (primary PCI, p=0.03) (Widimsky et al 2007). In DANAMI-2, after 3 years the non-significant trend towards a lower rate of composite end-point after primary PCI was consistent across symptom duration from short (<2 hours) to intermediate (2 to <4 hours) and relatively long (≥4 hours) (Busk et al. 2007).

The PCI-related delay is usually presented as the door-to-balloon time minus the door-to needle time. A meta-analysis of 22 randomized trials (CAPTIM not included) with an overall PCI-related delay of 55 (37-74) minutes observed a 30-day death rate of 7.9% in FT patients and 5.3% in those randomized to primary PCI (p<0.001) (Boersma and The Primary Coronary Angioplasty vs. Thrombolysis Group 2006). In patients randomized to FT, 30-day mortality increased two-fold as the presentation delay increased from less than 1 to over 6 hours (p<0.001). A similar, yet non-significant, trend was observed in patients assigned to primary PCI (p=0.06). Overall, primary PCI patients had 37% relative lower odds of 30-day mortality than those randomized to FT after multi-level covariate adjustment (OR 0.63, CI 0.42-0.84, p<0.001). According to presentation delay, the treatment effect consistently favoured primary PCI in all subgroups. The absolute mortality reduction by primary PCI increased from 1.3% in patients randomized in the first hour after symptom onset to 4.2% in those randomized after 6 hours. Consequently, with increasing delay, the number needed to treat to prevent one death during the 30-day follow-up decreased from 77 to 24 patients. The balance of the treatment effect in this meta-analysis remained with primary PCI when its association with PCI-related delay was examined, particularly if the delay was 35 minutes or less. According to another meta-analysis using data from 23 randomized trials, the absolute survival benefit attained with primary PCI compared with FT decreased by 0.94% for every additional 10 minutes of PCI-related delay

(Nallamothu and Bates 2003). Overall, the 2 reperfusion strategies appeared to become equivalent in terms of mortality after a PCI-related time delay of 62 minutes. However, the lack of survival benefit with delayed primary PCI would not diminish the clinical importance of fewer re-infarctions, strokes and urgent revascularizations or shorter hospital stay.

There are no data from large randomized studies evaluating outcome for patients with a PCI-related delay (defined as median time from randomization to the first balloon inflation minus median time to the first injection of the fibrinolytic agent) >120 minutes (Boersma and The Primary Coronary Angioplasty vs. Thrombolysis Group 2006).

7.4 Recent recommendations of the European Society of Cardiology

Reperfusion therapy is indicated in all patients with a history of chest pain/discomfort of <12 hours´ duration and associated with ST-segment elevation or (presumed) new LBBB on ECG (Van de Werf et al. 2003).

According to the guidelines of the European Society of Cardiology, primary PCI is a class I indication in patients with acute STEMI who can undergo the procedure performed by an experienced team <90 minutes after first medical contact, in patients in shock and those with contraindications to FT. For patients admitted to a hospital without catheterization facilities on site, a careful individual assessment should be made of the potential benefits of mechanical reperfusion in relation to the risk and treatment delay involved in transportation to the nearest interventional catheterization laboratory (Van de Werf et al. 2003).

In the absence of contraindications and if primary PCI cannot be performed by an experienced team within 90 minutes after first medical contact, pharmacological reperfusion is a class I indication and FT should be initiated as soon as possible. Pre-hospital initiation of FT is preferred if appropriate facilities exist (Van de Werf et al. 2003).

However, the use of primary PCI as the treatment of choice for all patients with STEMI has not become routine. The explanation is complex: logistic difficulties attending such an approach (Nallamothu et al. 2005, McNamara et al. 2006), wide variation in PCI results between high- vs. low-volume centres (Christian et al. 1998, Canto et al. 2000, Vakili et al. 2001) and the possible deleterious effects of substantial treatment delay on outcome, myocardial salvage and resulting LV function (Weaver et al. 1993, Rawles 1997, van 't Hof et al. 1998a, De Luca et al. 2003, De Luca et al. 2004).

7.5 Coronary artery bypass surgery

The number of patients who need coronary artery bypass surgery in the acute phase of STEMI is limited. The procedure may be indicated when PCI has failed, when there has been a sudden occlusion of a coronary artery during catheterization, if PCI is not feasible, in selected patients in cardiogenic shock, or in association with surgery for a ventricular septal defect or mitral regurgitation due to papillary muscle dysfunction and rupture (Van de Werf et al. 2003). Some patients with STEMI who undergo primary PCI are found to have severe multivessel coronary artery disease. After the urgent restoration of antegrade flow in the IRA, the preferred management – medical, percutaneous or surgical – of the care of these patients, including its timing, is uncertain.

AIMS OF THE STUDY

The aims of the present study were:

1. to compare lead-specific computer-based ECG analysis with manual ECG measurements and to define values of computer-based measurements which would correspond to manually-measured clinical cut-off values for significant ST-segment deviation (**I**);

2. to develop and validate a computer model for anatomical interpretation of anterior AMI using manual ECG analysis as the golden standard in patients with suspected ACS (**II**);

3. to assess the value of ECG patterns in predicting the occlusion site on the LAD in relation to the diagonal side branches, to investigate the value of the ECG in identifying the LAD as the culprit artery and the impact on clinical outcome of ECG and angiographic signs of proximal vs. distal LAD occlusion (**III**);

4. to investigate the distribution of two distinct ECG patterns, the pre-infarction syndrome and evolving MI in the acute infarct process, and the impact of ECG features on outcomes of patients treated with primary PCI or FT (**IV**).

MATERIALS

1. Patients

The study populations for studies **I** and **II** were collected in Turku University Central Hospital and for studies **III** and **IV** from 29 hospitals in Denmark.

1.1 Studies I and II

The original study population comprised 531 consecutive patients admitted to the emergency room in Turku University Central Hospital between May 2000 and July 2001 and evaluated for suspected MI.

The ECGs used in study **I** were collected in 69 cases. The criteria for inclusion were the existence of a digitally recorded ECG at admission and an angiogram performed during the hospital stay. Exclusion criteria were LBBB (n=1) and pacemaker ECG (n=3).

For the purposes of study **II**, patients with a digitally recorded ECG at admission (n=369) were selected. Those with LBBB (n=25), LVH (n=26), pathological Q wave (n=47), wide QRS complex (n=42), pacemaker ECG (n=9) or poor technical ECG quality (n=4) were excluded. All exclusions were made by manual interpretation. A total of 216/369 (59 %) patients were included in the final study group.

1.2 Studies III and IV

In the DANAMI-2 patients from 24 referral hospitals without angioplasty facilities and 5 invasive-treatment hospitals with such facilities and on-site surgical back-up were enrolled from December 1997 to October 2001. Those with MI with ST-segment elevation were randomly assigned to fibrinolysis or primary angioplasty. Patients admitted to a referral hospital underwent randomization while they lay on the ambulance stretcher with the crew waiting. Randomization was done by telephone. Transfer to the nearest angioplasty center had to be completed within

three hours. A physician accompanied the patient. All ambulances had resuscitation equipment. The patients were transported directly to the catheterization laboratory.

For inclusion in the DANAMI-2 study the requirements were ischemic chest discomfort for ≥30 minutes, time from onset of symptoms ≤12 hours at randomization, and ECG with cumulated ST elevation ≥4 mm measured at the J-point (≥2 mm in at least 2 of leads I, aVL, V_1-V_6 or ST elevation ≥1 mm in all 4 leads II, III, V_5-V_6 or ST elevation ≥2 mm in at least 2 of leads II, III, V_5-V_6) (Andersen et al. 2003a).

Exclusion criteria included standard contraindications for fibrinolysis. Exclusion criteria for primary angioplasty were sepsis, aortic aneurysm with pendulating thrombus, no femoral pulses or bilateral femoral vascular grafts, previous coronary bypass grafting, severe renal failure with serum creatinine >250 μmol/L, and diabetes treated with Metformine within the last 48 hours. Furthermore, the expected time between randomization and arrival in the catheterization laboratory had to be <3 hours for patients randomized at referral hospitals and <2 hours for those randomized at invasive hospitals. Patients with acute MI (Q wave or non-Q wave) within the last 30 days were excluded. Also, patients with a high risk linked with ambulance transportation (cardiogenic shock or severe heart failure with severe hypotension [systolic blood pressure <65 mmHg], persistent life-threatening arrhythmias, or need for mechanical ventilation) were excluded from randomization (n=109). There was no upper age limit (Andersen et al. 2003a).

In the present study the end-point was a composite of mortality, clinical re-infarction and disabling stroke at 2.7 years' (median, inter-quartile range [IQ] 1.9-3.6) follow-up. Clinical re-infarction was defined as any new MI occurring after the index infarct according to the predetermined criteria unrelated to a PCI/coronary artery bypass surgery (Andersen et al. 2003a). The patients were entered into the database immediately after randomization. The primary end-point was at 30 days and during this period all end-point patient data were entered continuously. After a minimum follow-up of 2 years the status on admission (AMI and stroke) and death were obtained from various registries. Follow-up information was available for all patients utilizing the national social security number-based registries.

The DANAMI-2 trial randomized 1572 patients. The present study required re-analysis of all the qualifying ECGs in the trial. It was not possible properly to confirm the patient study number and/or timing of the ECG in 19 cases, and 31 randomization ECGs were never sent to the core laboratory at Tampere University Hospital. Ultimately 1522 patients were included in this study. Patients with ECG confounders such as LBBB, LVH, pacemaker ECG and RBBB in association with left anterior hemiblock were excluded. Also patients with ECG signs of lateral

STEMI were not included in view of the small number of such cases (n=23). Pure lateral STEMI seldom presents with massive ST deviations (≥2 mm ST-elevation in at least 2 of leads I, aVL, V_5-V_6). Finally, 1300 patients with anterior (n=624) or inferior (n=676) infarct locations were included. They were divided into two subgroups based on ECG findings: pre-infarction syndrome (n=952) and evolving MI (n=348). In addition the EMI group was graded according to ECG signs of reperfusion. The more specific flow chart in Figure 4 illustrates the ECG subgroups and treatment of the patients.

2. Ethical aspects

2.1 Studies I and II

The Ethics Committee of Turku University Central Hospital accepted the study protocol and written consent was obtained from all study participants.

2.2 Studies III and IV

The study was approved by the National Ethics Committee of Denmark. All eligible patients provided written informed consent.

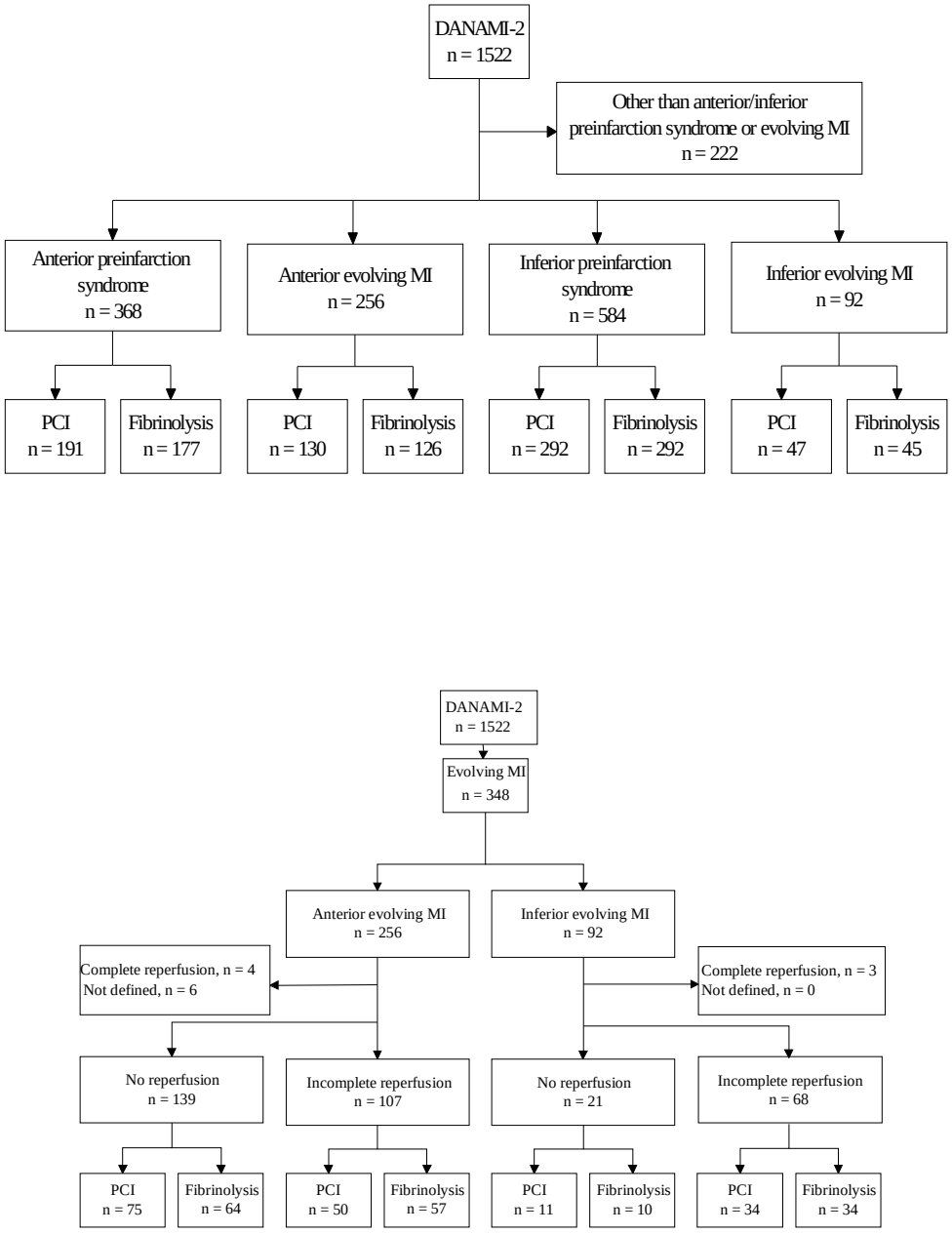


Figure 4. Flow charts showing the subgroups of patients defined by the electrocardiogram in the whole study population (upper) and in the evolving myocardial infarction group (lower).
MI, myocardial infarction; PCI, primary percutaneous coronary intervention.

METHODS

1. Studies I and II

1.1 ECG analysis

The ECGs were recorded on a Marquette 12SL machine (Marquette Electronics Inc., Milwaukee, Wisconsin) used routinely in Turku University Central Hospital. Paper copies of the 69 (**I**) or 216 (**II**) ECGs recorded on admission were independently interpreted, retrospectively and in random order by two investigators at Tampere University Hospital. The ECG analysis was performed without knowledge of the results of computerized interpretation or knowledge of the patients' clinical details. Single measurement of J point, ST segment and T wave changes were taken separately from all 12 leads with the aid of a hand-held magnifying lens. ST-segment deviation was measured at 80 ms after the J point, while the isoelectric line was determined by drawing a line between subsequent PQ segments. Maximal T-wave deviation from the isoelectric line was measured at least 120 ms after the J point. All manual measurements were rounded off to the nearest 0.5 mm.

As part of the coding package, the Marquette 12SL offers a data matrix (Elko and Rowlandson 1992). This is a matrix with the 12 leads presented as rows and selected attributes of the P, Q, R, S waves and displacements of the ST segment at the J point and at the midpoint of the ST segment, and the amplitudes of T waves as columns. The data presented in the data matrix describe the median complex generated by the Marquette 12SL system. The use of this matrix in a personal computer has been previously described (Porela et al. 1999).

Manually measured deviations at the J point, the ST segment and the T wave were compared with those measured by the computer and expressed in the data matrix, excluding lead aVR. Three numerical cut-off points were chosen for comparison based on their clinical importance: 1) 2 mm is the cut-off point for reperfusion therapy in anterior MI, 2) 1 mm in inferior MI and 3) 0.5 mm is considered a clinically significant ST deviation. After comparing

all leads except aVR, leads V_2, V_3 and LIII were selected for additional statistical analysis as being of most critical importance in anatomical interpretation of the ECG.

1.1.1 Definition of the site of occlusion

Manual anatomical interpretation of the ECG was made in cases with anterior STEMIs. The anatomical classification of the LAD occlusion was made on the following criteria: 1. the LAD was interpreted as the IRA if maximal ST-segment elevation (≥2 mm) was present in leads V_2–V_3; 2. a proximal lesion in the LAD was defined as ST-segment elevation ≥0.5 mm in lead aVL and ST depression ≥0.5 mm in LIII. All other ECG morphologies were classified as distal occlusion.

1.2 PC interpretation program

An automatic PC interpretation program for the detection and anatomical classification of LAD occlusion was constructed using the above-mentioned criteria and applied to the data on the 216 patients with suspected ACS. In addition to uncorrected cut-off points (as expressed in the data matrix) , we used corrected cut-offs for the computer program to detect equivalents of manual ST elevations of ≥2 mm, 1 mm and 0.5 mm.

1.3 Coronary angiography

Selective coronary angiography was performed during hospitalization in 69 out of 216 cases with multiple projections (**II**). The median time from admission to angiography was 6 days. The indication for angiography was clinical in all cases. The site and severity of luminal narrowing in each coronary artery was defined retrospectively and in random order by two investigators blinded to the clinical and ECG data. If possible, the site of the culprit lesion (defined as complete obstruction, residual thrombus or ulcerated plaque) was determined. A culprit lesion in a proximal part of the LAD artery was defined as appearing before the first diagonal branch. A significant coronary artery stenosis was defined by visual estimation as a >50% luminal diameter narrowing involving a major coronary vessel or side branch.

2. Studies III and IV

All randomization ECGs were analyzed by three investigators blinded to the clinical data and angiographic findings in the independent core laboratory at Tampere University Hospital. Any disagreement between the investigators was resolved by consensus. One investigator at the core laboratory at Aalborg University Hospital analyzed all coronary angiograms blinded to the clinical and ECG data.

2.1 ECG measurements

2.1.1 Measurement point

The ST segment was measured manually at the J point with the TP segment as the isoelectric line. The T wave was considered positive or negative if it was 0.5 mm or more above or below the isoelectric line, measured more than 120 ms after the J point.

2.1.2 Q wave

Pathological Q waves were defined as follows: 1) in leads V_{1-3} any Q wave ≥30 ms in duration, 2) in leads I, II, aVL, aVF, V_{4-6} a Q wave ≥1 mm in height and ≥30 ms in duration in ≥2 adjacent leads and 3) in leads V_{1-2} R wave duration >40 ms and R/S ratio >1 in the absence of pre-excitation, right ventricular hypertrophy or RBBB (Perloff JK 1964, Cannon CP et al. 2001).

2.1.3 MI localization

Anterior MI was defined as ST elevation ≥2 mm maximally in at least two contiguous chest leads V_2-V_4. Inferior MI was defined as ≥1 mm ST elevation in ≥2 of the extremity leads II, III and aVF. In cases of concomitant ST elevation in the precordial leads V_1-V_3, patients were included in the inferior MI group if the sum of ST elevation was higher in leads V_1-V_2 than in leads V_2-V_3. Also patients with inferior ST elevations (in ≥2 leads) with concomitant ST

elevation in leads V_4-V_6 but not in leads V_1-V_3 were included. Lateral infarcts were not analyzed as a separate group.

2.1.4 Culprit artery and site of occlusion

The LAD was defined as the culprit artery in patients with maximal ST elevation ≥2 mm in at least two contiguous leads V_2-V_4. In the analysis of occlusion site with respect to side branches we excluded patients with evolving MI.

Three pre-specified ECG patterns were compared to determine the level of LAD occlusion based on the 12-lead ECG. Occlusion in the proximal part of the LAD was defined by 1) concomitant ST elevation ≥0.5 mm in lead aVL (aVL+ pattern) (Figure 5A) or 2) either ST elevation ≥0.5 mm in lead aVL or any ST elevation in lead aVR (aVR+ pattern) (Figure 5B).

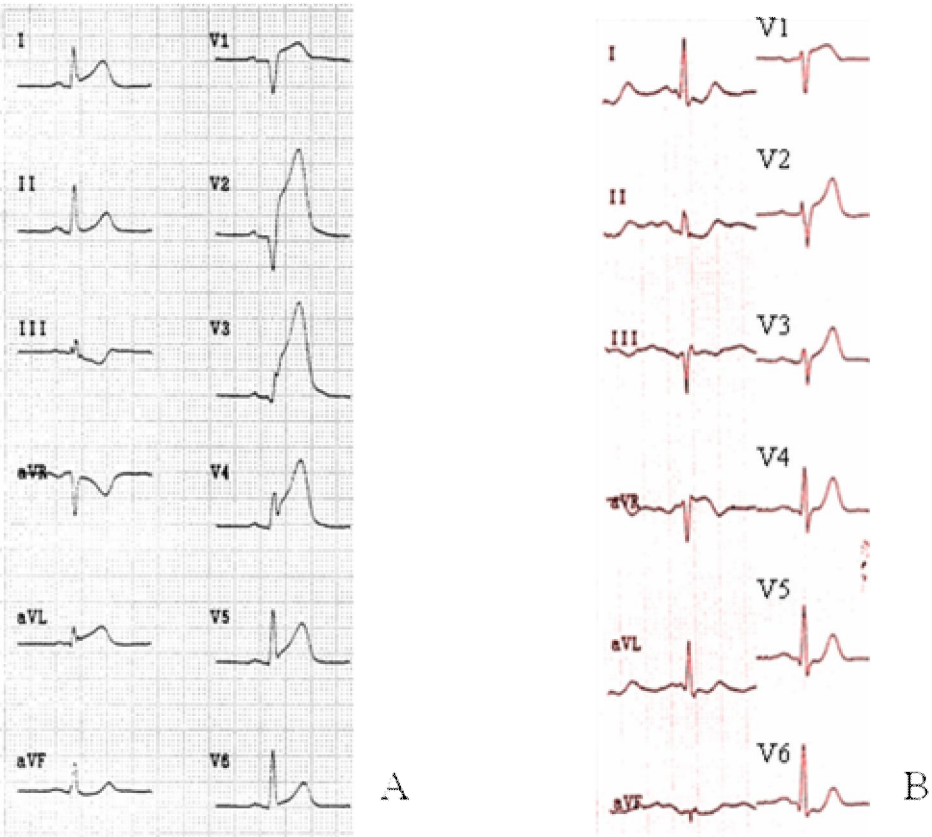


Figure 5. Maximal ST-segment elevation in leadsV_2-V_3 in both ECGs indicates that the left anterior descending coronary artery is the infarct-related artery. (A) The presence of ST-segment elevation ≥0.5 mm in lead aVL and ST-segment depression in lead III as a reciprocal change is a sign of an occlusion proximal to the first diagonal side branch, aVL+ pattern. (B) There is ST-segment elevation in lead aVR; this is the aVR+ ECG pattern.

The hypothesis was that occlusion in a big wrap around the apex artery may result in ischemia of two electrically opposite areas, the anterior and the inferior. This in turn may attenuate the ST elevations in the electrically opposite leads aVL and III, resulting in an isoelectric or even depressed ST segment in lead aVL despite a proximal LAD occlusion. According to our hypothesis we additionally defined proximal LAD occlusion as an aVR+ pattern excluding patients (n=9) with concomitant ST elevation ≥1 mm in all inferior leads (proximal pattern). All other ECG morphologies were classified as distal occlusion. The ECG findings were correlated to those of coronary angiography performed in the acute phase.

2.1.5 ECG definitions of pre-infarction syndrome and evolving myocardial infarction

The *pre-infarction syndrome* was defined as ST-segment elevation fulfilling the afore-mentioned criteria for anterior or inferior MI, but without pathological Q waves or inverted T waves in the leads with ST elevation (Figure 6A).

Evolving MI was defined by appearance of pathological Q waves and/or negative or biphasic T waves. These ECG changes usually represent myocardial necrosis or reperfusion. For convenience the term negative T wave is also used for patients with biphasic T waves with a ≥0.5 mm negative terminal portion. *No reperfusion* was defined as ST elevation with a positive T wave (Figure 6B). *Incomplete reperfusion* was defined as ST elevation with inversion of the T wave (Figure 6C). *Complete reperfusion* was defined as an isoelectric or minor ST segment with a completely inverted T wave (Figure 6D).

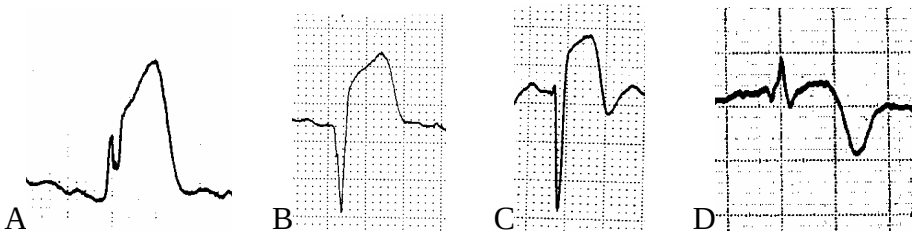


Figure 6. The distinct electrocardiographic patterns of the pre-infarction syndrome and evolving myocardial infarction (MI) in lead V_3. (A) The pre-infarction syndrome: an elevated ST segment and a peaked T wave without Q wave. (B) Evolving MI without ECG signs of reperfusion: a deep Q wave, an elevated ST segment and a positive T wave. (C) Evolving MI with incomplete reperfusion: ST elevation, a biphasic T wave (negative terminal portion). (D) Evolving MI with complete reperfusion: minor ST elevation, negative T wave.

2.2 Coronary angiography

One investigator at the core laboratory at Aalborg University Hospital in Denmark analyzed all angiograms blinded to the clinical and ECG data. The site and severity of luminal narrowing in each coronary artery was defined. A significant coronary artery stenosis was defined by visual estimation as a >50% luminal diameter narrowing involving a major coronary vessel or side branch. The culprit artery was defined. When more than one lesion was present in the artery, the site of the culprit lesion was determined by the appearance of complete obstruction of the artery or by the more detailed angiographic characteristics of the lesion, including the presence of either residual thrombus or ulcerated plaque. The culprit lesion was considered proximal when located before a medium- to large-sized (≥1.5 mm) diagonal branch.

3. Statistical methods

Categorical variables were expressed as numbers of patients or percentages and continuous variables as medians followed by IQ range. Statistical significance (two-tailed p-value <0.05) was assessed by the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney test for numerical variables. Sensitivity, specificity and positive and negative predictive values were calculated. Confidence intervals (CI) were calculated at the 95% significance level. The event rates were presented per 100 person-years with CIs. The relative risks (RR) were analyzed by the Mantel-Haenszel method. Composite end-point data between ECG sub-groups were plotted as Kaplan-Meier curves. Comparison between groups was made using the log rank statistic. Cox regression analysis was used to test the prognostic significance of baseline and ECG variables concerning composite end-points at follow-up. Hazard ratios (HR) were presented. Multivariable analyses (**IV**) were carried out by entering the following variables: age ≥75 years, Killip class on admission, heart rate >100 beats per minute, anterior location of infarction, time to treatment >4 hours, weight <67 kg, history of diabetes, history of hypertension, smoking status, gender, lipid-lowering medication, aspirin medication, ECG pattern and treatment group. The effect of ECG pattern on the composite end-point was determined by evaluating the interaction term (ECG pattern-treatment group).

Agreement between categorical assessments (e.g. ST-segment elevation ≥2 mm) was described by Kappa (κ) statistics. Kappa describes the strength of agreement as a proportion of

the possible scope for doing better than chance. Kappa has a maximum of 1.00 for perfect agreement, whereas 0 indicates no agreement better than could be expected by chance (Altman 1991). A generally accepted mode of κ value interpretation is illustrated in Table 6.

Table 6. The principles of kappa value interpretation.

Value of κ	Strength of Agreement
≤0.20	Poor
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Good
0.81-1.00	Very good

κ, kappa

The optimal cut-off points for the computer program to detect true ST-segment deviation were tested using manual measurements as gold standard. The analysis commenced by constructing scatter plots of the measured ST-segment deviations. Thereafter cross-tabulations were performed in an attempt to increase sensitivity for the detection of actual ST elevation without reducing specificity from 98%.

The Bland-Altman statistical method was used in assessing agreement between the two methods of electrocardiographic measurements (Bland and Altman 1986). Firstly, inter-observer agreement was compared between the two cardiologists, and secondly, agreement between computerized measurements and one cardiologist. The calculated mean difference between measured values ±2 standard deviations of the differences was considered the limit of agreement. The difference between two measurements against their mean was plotted. Bland-Altman plots were created to show differences in measurements between the two cardiologists and one cardiologist vs. the computer with the means of the measurements.

All calculations were performed with the SPSS 12.0 or 12.5 statistical package and the Stata 8.2 for Windows.

RESULTS

1. ECG measurement agreements

1.1 Inter-observer agreement

The inter-observer agreements between the two cardiologists were very good in respect of determination of ST-segment elevation ≥2 mm and 1 mm (κ=0.91 and κ=0.85, respectively).

In lead-specific measurements, the inter-observer reliability in the determination of ST-segment deviation ≥2 mm in leads V_2, V_3 and ≥1 mm in lead III was very good (κ=0.94, 0.93 and 0.80, respectively). The agreement between the two cardiologists was also very good with regard to the determination of ST-segment depression ≥0.5 mm in lead III (κ=0.86).

Bland-Altman analysis demonstrated excellent limits of agreement between the two cardiologists when comparing J-point, ST-segment and T-wave amplitude measurements (Figure 7).

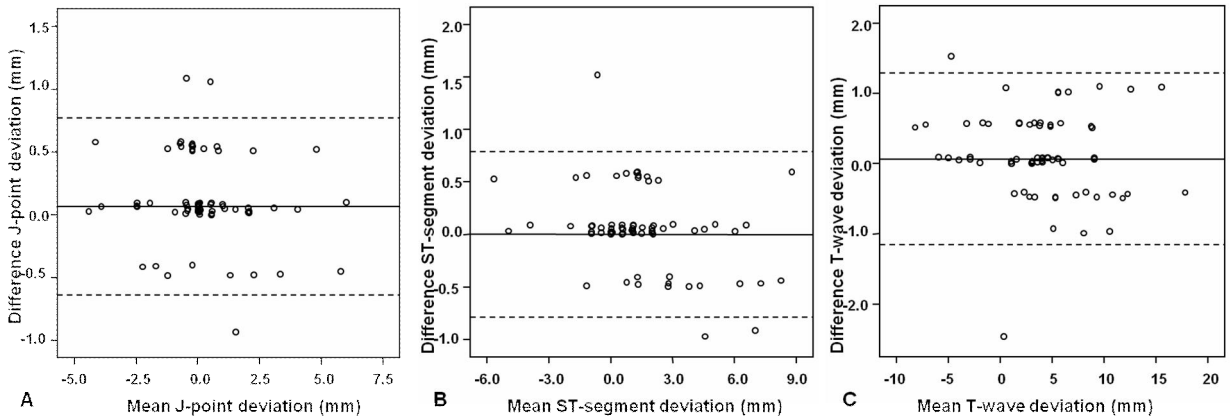


Figure 7. Bland-Altman diagrams of J-point, ST-segment and T-wave deviations, demonstrating mean difference (——) and limits of agreement (▪▪▪▪), n=69, between two cardiologists as compared to measurements of J-point deviation (A), of ST-segment deviation (B) and of T-wave deviation in lead V_3 (C).

1.2 Manual versus computer agreement

ST-segment deviations were measured manually and by computer in a total of 759 leads, excluding lead aVR. For the entire ECG data basis, the agreement between the manual and the computer measurements in the determination of ST-segment elevation ≥2 mm was good (κ=0.63). The correlation between the manual and the computer measurements in the determination of ST-segment deviation ≥1 mm was moderate (κ=0.51).

The cardiologist and the computer interpreted ST-segment elevation ≥2 mm in lead V_3 with very good agreement (κ=0.85) and in lead V_2 with good agreement (κ=0.72). In lead III agreement in the determination of ST-segment elevation ≥1 mm was moderate (κ=0.52), but was better for measurements of ST depression ≥0.5 mm (κ=0.79).

When the ST-segment elevation was 1 mm measured manually at 80 ms after the J point (n=163 leads), the corresponding mean of the computer measurements of the ST deviation was 0.53 mm (SD ± 0.35 mm). Computer-based mean ST-segment deviation was 1.52 mm (SD ± 0.48 mm) in 61 leads with manually measured ST-elevations of 2.0 mm. As a whole, when compared with manual analysis, the computer underestimated ST-segment deflection (Figure 8).

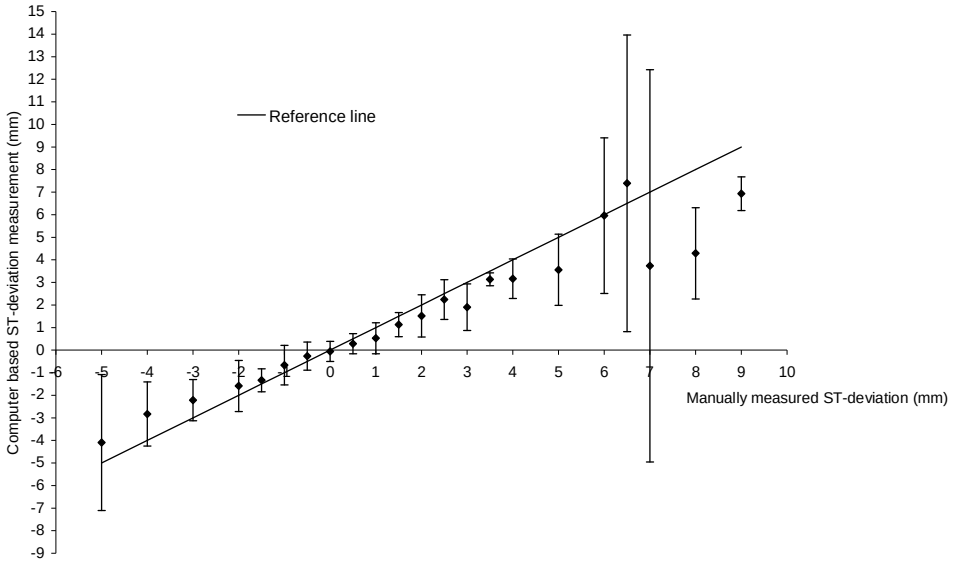


Figure 8. Variability of measured ST-segment deflections between cardiologist and computer-based measurements (n=759). Manually measured and computer based ST deviation measurements are given in millimetres (mm). The box represents the mean of the automated measurements and the error bars the standard error of mean.

Bland-Altman analysis of measured deviations of the J point and the T wave from cardiologist and computer demonstrated acceptable limits of agreement. However, the test showed clinically unacceptable limits of agreement comparing measurements of ST-segment deviations between cardiologist and computer (Figure 9).

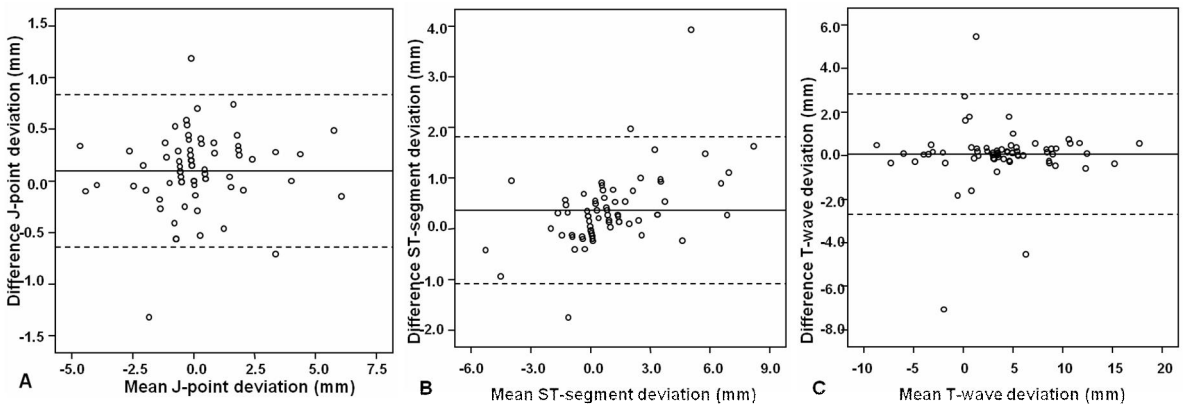


Figure 9. Bland-Altman diagrams of J-point, ST-segment and T-wave deviations, demonstrating mean difference (——) and limits of agreement (▪▪▪▪), n=69, between cardiologist and computer-based measurements as compared to measurements of J-point deviation (A), of ST-segment deviation (B) and of T-wave deviation in lead V_3 (C).

1.3 Corrected cut-off points for computer

Different cut-off points to demonstrate optimal computerized value in millimeters were tested to detect true ST-segment elevation ≥2 mm, 1 mm and 0.5 mm, respectively. The clinically optimal, corrected cut-off point for computer-based deviation to separate true ST-segment elevation ≥2 mm was 1.15 mm, with a sensitivity of 89% and a specificity of 98%. The corrected cut-off point to find ST elevation ≥1 mm was 0.45 mm with a sensitivity of 76% and a specificity of 98%. The optimal computerized cut-off value to detect the equivalent of manually registered ST-segment elevation ≥0.5 mm was found to be 0.35 mm, with a sensitivity of 79% and a specificity of 98%.

2. Computerized anatomical ECG interpretation

Manual anatomical interpretation of the ECG indicated that the LAD was the IRA in 12 of the 216 patients (6 %) with suspected ACS (**II**). The site of the occlusion was proximal in 7 (58 %) of these patients. The manual analysis was used as golden standard.

The use of ST-segment corrections improved the ability to determine the LAD as the culprit vessel and the level of occlusion in the LAD. The sensitivities, specificities and the κ values of the computer program in detecting various LAD occlusions were better with the corrected than uncorrected ST segment cut-off points (Table 7).

Table 7. Sensitivity, specificity and kappa values of uncorrected and corrected computer program in detecting site of occlusion on the left anterior descending coronary artery in patients with acute coronary syndrome when using manual interpretation as gold standard, n=216.

	Uncorrected computer program			**Corrected computer program**		
Site of occlusion	**Se %**	**Sp %**	**Value of κ**	**Se %**	**Sp %**	**Value of κ**
LAD	58	99	0.65	67	99	0.71
Proximal LAD	86	100	0.65	86	100	0.72
Distal LAD	20	99	0.65	40	99	0.72

Se, sensitivity; Sp, specificity; κ, kappa; LAD, left anterior descending coronary artery

3. Culprit lesion in the LAD (III)

3.1 LAD as a culprit vessel based on ECG

The pre-specified ECG criteria for LAD occlusion (n=298) had a sensitivity of 87% and specificity of 96% to predict the angiography findings. Also the positive and negative predictive values were high, 95% and 88%, respectively.

3.2 Level of occlusion in the LAD based on ECG

The sensitivity, specificity and predictive values of the different ECG patterns (n=155) to predict the level of occlusion with respect to diagonal side branches are listed in Table 8. Proximal occlusion of the LAD could be predicted with a sensitivity of 94% and specificity of 49% by the pre-specified proximal pattern. This pattern evinced good positive (85%) and negative predictive values (71%) in predicting a proximal occlusion in the LAD on coronary angiography. The median time from onset of symptoms to randomization ECG was 1 hour and 35 minutes (IQ 58 min – 2h 35 min) and to PCI (first balloon inflation) 3 hours and 12 minutes (IQ 2h 35 min – 4h 20 min). Accordingly, the median delay from the ECG recording to the angiogram was less than 97 minutes.

Table 8. The sensitivity, specificity, positive and negative predictive value for the different ECG patterns to predict proximal occlusion of the left anterior descending coronary artery in patients with acute anterior myocardial infarction (concomitant ≥2 mm ST elevation maximally in leads V_2-V_4).

ECG pattern	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
aVL+	82	50	84	45
aVR+	87	50	85	55
Proximal	94	49	85	71

aVL+ pattern, ST elevation ≥0.5 mm in lead aVL; aVR+ pattern, either aVL+ pattern or any ST elevation in lead aVR; Proximal pattern, aVR+ pattern excluding patients with ST elevation ≥1 mm in all inferior leads; ECG, electrocardiogram; PPV, positive predictive value; NPV, negative predictive value.

3.3 Proximality of the LAD occlusion – impact on outcome

In patients treated with primary PCI, proximal LAD occlusion as identified by ECG criteria (proximal pattern) was not associated with poorer clinical outcome than distal occlusion at 30 days and at 2.7 years (composite end-point 9 vs. 13%, p=0.57 and 21 vs. 17%, p=0.65, respectively). Neither was any statistically significant difference observed in mortality, clinical re-infarction and disabling stroke at 30 days and at 2.7 years between angiographically defined proximal vs. distal occlusion (12 vs. 17 %, p=0.39 and 23 vs. 26 %, p=0.62, respectively).

In the entire study group at 2.7 years' follow-up, the rate of the composite end-point was equal between the primary PCI and the FT groups with a proximal LAD occlusion defined by ECG (21 vs. 18 %, p=0.7, respectively).

4. Pre-infarction syndrome and evolving myocardial infarction

4.1 Baseline data

The baseline data on patients are presented in Table 9 (**III, IV**). The median time from the onset of symptoms to recording of the randomization ECG and time to PCI was shorter in those with PIS compared to those with EMI. Those with PIS were younger and more often smokers compared with patients with EMI. The patients with EMI more often had diabetes and angiotensin-converting enzyme inhibitor medication, and they also had faster heart rates, higher systolic blood pressure and lower ejection fraction than those with PIS. Otherwise, the baseline characteristics of the patients were similar.

4.2 Localization of MI and distribution of ECG patterns

Of the 1522 patients, 624 (41%) had an anterior STEMI and 676 (44%) an inferior STEMI as defined on our ECG criteria. The ECG pattern of PIS was more common than EMI in patients with acute anterior STEMI (59 vs. 41%, respectively). In inferior infarctions the ECG pattern of EMI was rare (14%).

4.3 Correlation with coronary angiography

The distribution of angiographic findings in the groups with different ECG patterns is presented in Table 10. Only very few patients (4%) with anterior MI had other than the LAD as the culprit artery, while in inferior MI, most cases were caused by either RCA (74%) or LCX (17%) occlusions.

Table 9. Baseline characteristics according to different ECG patterns (**III, IV**).

Baseline characteristics	**Anterior PIS n=368 n (%)**	**Anterior EMI n=256 n (%)**	**Inferior PIS n=584 n (%)**	**Inferior EMI n=92 n (%)**	**P-value**
Age (yr)[a]	62 (51-74)	65 (57-75)	62 (53-71)	63 (54-73)	<0.001
Gender (males)	272 (74)	189 (74)	409 (70)	76 (83)	0.07
Hypertension	74 (20)	56 (22)	105 (18)	27 (29)	0.12
Diabetes	26 (7)	28 (11)	23 (4)	9 (10)	0.003
Current smoker	202 (55)	133 (52)	385 (66)	42 (46)	<0.001
Previous MI	40 (11)	26 (10)	47 (8)	17 (19)	0.02
Previous PCI	11 (3)	8 (3)	17 (3)	4 (5)	0.6
Previous stroke	7 (2)	10 (4)	17 (3)	2 (2)	0.6
Heart rate (beats/min)[a]	75 (64-86)	80 (68-95)	68 (58-80)	75 (62-87)	0.002
Systolic blood pressure (mmHg)[a]	138 (120-150)	140 (120-160)	130 (110-150)	135 (120-150)	<0.001
Medical treatment					
Aspirin	88 (24)	51 (20)	111 (19)	27 (29)	0.07
Beta-blockers	59 (16)	28 (11)	58 (10)	18 (20)	0.01
ACE-inhibitors	33 (9)	28 (11)	35 (6)	12 (13)	0.01
Ca antagonists	37 (10)	20 (8)	58 (10)	13 (14)	0.36
Nitrates	22 (6)	13 (5)	23 (4)	7 (8)	0.25
Diuretics	55 (15)	44 (17)	64 (11)	12 (13)	0.12
Lipid-lowering drugs	22 (6)	8 (3)	41 (7)	7 (8)	0.13
Coumarins	4 (1)	5 (2)	12 (2)	1 (1)	0.9
Time to randomization[a]	01:35 (00:54-02:47)	02:24 (01:20-04:43)	01:51 (01:04-03:03)	03:02 (01:36-04:57)	<0.001
Time to PCI/FT[a]	02:44 (02:00-04:00)	03:40 (02:27-06:02)	02:55 (02:10-04:14)	04:19 (02:37-06:17)	<0.001
Primary PCI	191 (52)	131 (51)	292 (50)	47 (51)	0.94
EF (echo)[a]	50 (40-55)	43 (35-50)	55 (50-60)	50 (45-60)	<0.001

[a]Variables are given as percentages or median values followed by inter-quartile ranges, time in hours and minutes. ECG, electrocardiogram; PIS, pre-infarction syndrome; EMI, evolving myocardial infarction, MI, myocardial infarction; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; Ca, calcium; FT, fibrinolytic therapy; EF, ejection fraction; Echo, echocardiography

Table 10. The infarct-related artery in patients treated with primary angioplasty according to different ECG patterns.

Culprit lesion	**Anterior PIS n=171**	**Anterior EMI n=120**	**Inferior PIS n=266**	**Inferior EMI n=43**
Left anterior descending	165	113	4	2
Left circumflex	1	1	49	3
Right	2	2	193	36
Diagonal branch	2	2	2	-
Left obtuse marginal	1	2	14	2
Left main	-	-	2	-

ECG, electrocardiogram; PIS, pre-infarction syndrome; EMI, evolving myocardial infarction

4.4 Correlation with clinical outcome

The event rate for the composite end-point (death, MI, stroke) was higher in the EMI than in the PIS group (11.4 [9.4-13.9] and 6.9 [6.0-8.0] per 100 person-years, respectively, RR 1.6, p<0.001). The difference was explained by the higher mortality in the EMI than in the PIS group (8.3 [6.7-10.4] and 3.9 [3.2-4.7] per 100 person-years, respectively, RR 2.1, p<0.001)(Figure 10).

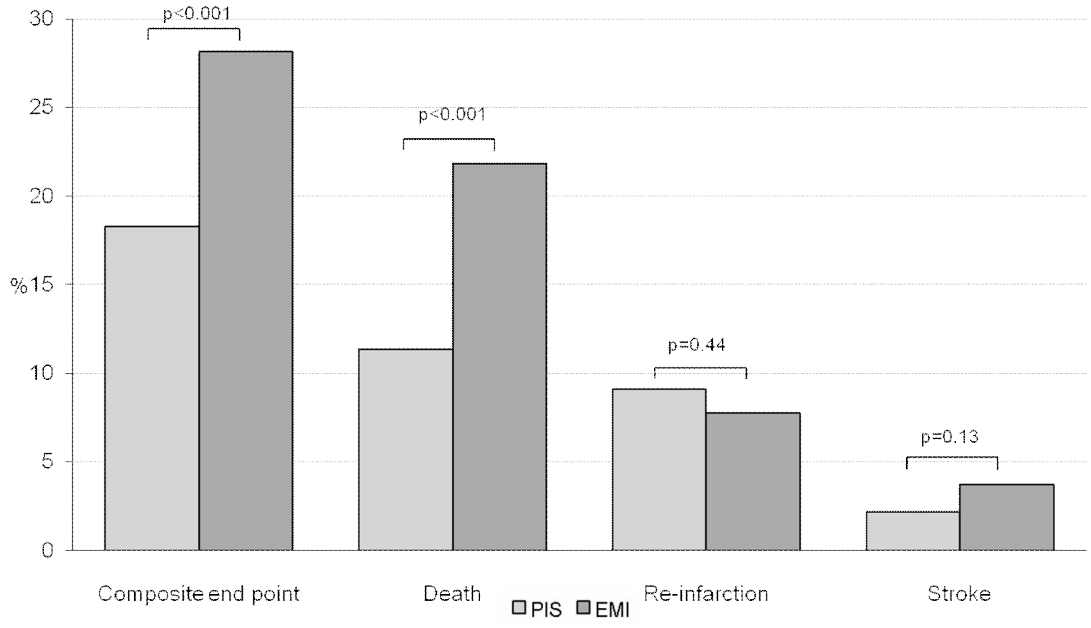


Figure 10. Composite and component endpoints at 2.7-year follow-up for patients with an ECG pattern of pre-infarction syndrome (PIS) or evolving myocardial infarction (EMI).

In multivariable analysis, the ECG finding of EMI gave a poor prognosis compared with the ECG finding of PIS. The other variables which provided independent prognostic information in multivariable analysis were age ≥75 years, aspirin treatment, lipid-lowering treatment, anterior MI and weight <67kg (Table 11). The interaction term indicated that the ECG pattern was independently predictive (p for interaction 0.167).

Table 11. Results of multivariable Cox proportional hazards model examining the relations of pre-specified variables to composite end-point at 2.7-year follow-up.

	Hazard ratio	95% CI	P-value
Age ≥75 years	2.849	2.132-3.802	<0.001
Killip class >1	1.414	0.958-2.092	0.081
Heart rate >100 bpm	1.499	0.994-2.262	0.667
Anterior MI	1.321	1.002-1.739	0.048
Time to treatment >4 hours	1.057	0.805-1.389	0.692
Weight <67 kg	1.484	1.072-2.053	0.017
Diabetes	1.486	0.982-2.252	0.061
History of hypertension	1.151	0.850-1.558	0.362
Current smoker	1.031	0.785-1.353	0.829
Male	1.092	0.797-1.497	0.582
Lipid-lowering treatment	0.399	0.192-0.826	0.013
Aspirin treatment	1.859	1.395-2.475	<0.001
Evolving MI on ECG	1.524	1.009-2.299	0.045
PCI treatment	0.984	0.637-1.522	0.942
Interaction term for ECG pattern and treatment group			0.167

CI, confidence interval; bpm, beats per minute; MI, myocardial infarction; ECG, electrocardiogram; PCI, percutaneous coronary intervention

4.5 Correlation with therapeutic approach

Among patients with PIS (n=952), the event rate of primary composite end-point was lower in those treated with primary PCI compared with FT at follow-up (5.5 [4.4-6.9] and 8.5 [7.0-10.4] per 100 person-years, respectively, RR=0.6, p=0.004) (Figure 11). The difference was explained by the lower re-infarction rate in the primary PCI than in the FT group (3.0 [2.1-4.3] and 6.8 [5.2-8.7] per 100 person-years, respectively, RR 0.5, p<0.001)(Figure 12). The number needed to treat with primary PCI to avoid one end-point event during the 2.7-year follow-up was 17 (CI 9-89).

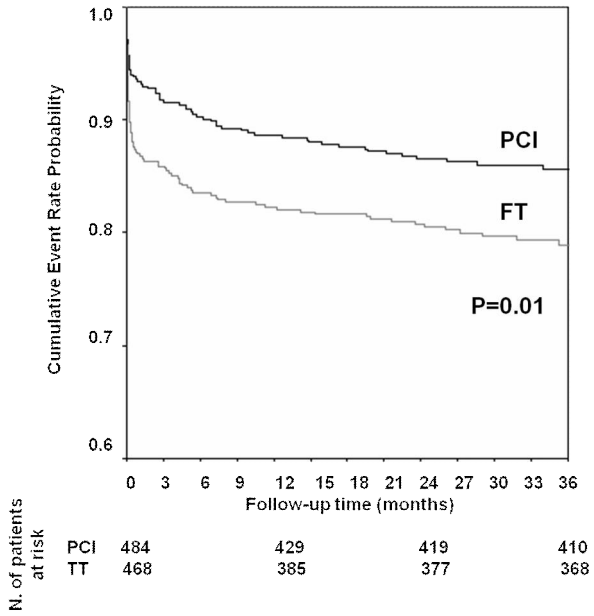


Figure 11. Kaplan-Meier curve showing freedom from cumulative events of primary composite end-point of death, clinical re-infarction or disabling stroke during follow-up in patients with the pre-infarction syndrome and treated with primary percutaneous coronary intervention (PCI) or fibrinolytic therapy (FT). P-values were calculated using the log-rank test.

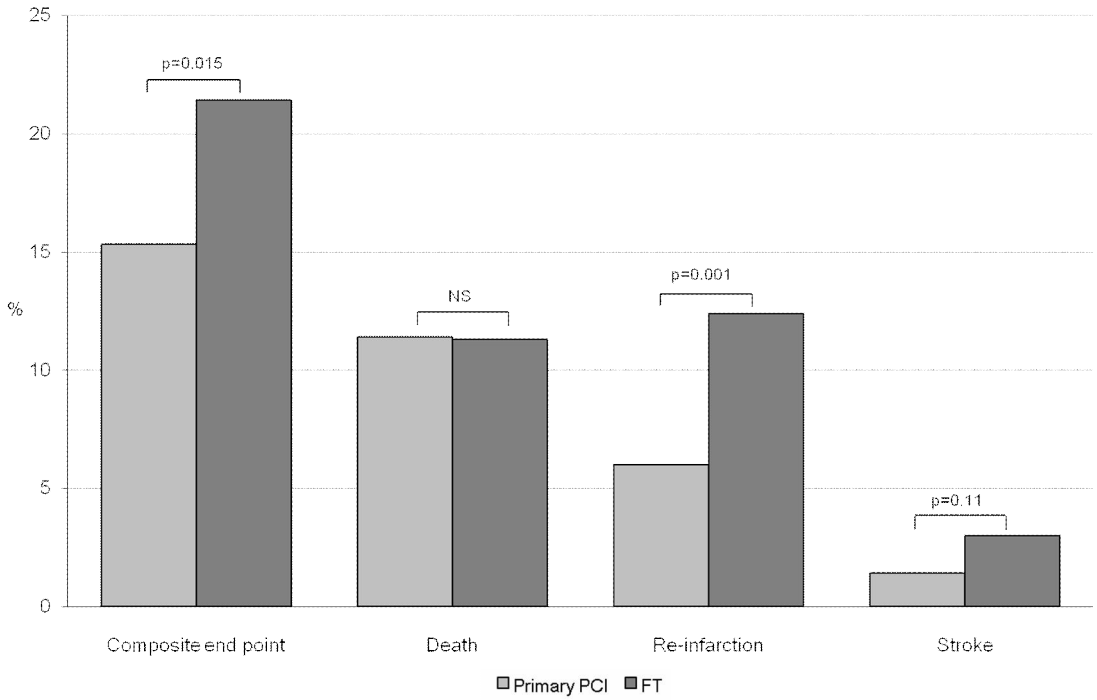


Figure 12. Composite and component end-points at 2.7-year follow-up in patients with the ECG pattern of pre-infarction syndrome who were randomized to primary percutaneous coronary intervention (PCI) or fibrinolytic therapy (FT).

There was no statistically significant difference in mortality, clinical re-infarction or disabling stroke at the 2.7-year follow-up between the two treatment arms among patients with EMI (n=348). In the anterior EMI group, however, patients with no signs of reperfusion on the ECG (n=139) treated with primary PCI had a better prognosis than those treated with FT (Table 12). In this group, the superiority of primary PCI over FT was attributable to a 51-percent reduction in the relative risk of composite end-point. The difference was explained by the lower mortality rate in the primary PCI group than in the FT group (5.7 [3.3-10.1] and 14.8 [9.6-22.7] per 100 person-years, respectively, RR 0.4, p=0.007)(Figure 13). The number needed to treat with primary PCI in order to avoid one death in a 2.7-year period was 6 (CI 3-39). In inferior EMI without ECG signs of reperfusion, the probability of reaching an end-point was higher with primary PCI than with FT.

4.6 Significance of Q waves

In the EMI group as a whole (n=348), there was no difference in composite end-points according to the presence (76%) or absence of Q waves (24%) on the ECG.

Table 12. Composite end-point at 2.7-year follow-up in patients with evolving myocardial infarction according to ECG signs of reperfusion.

ECG pattern	**Composite end-point (%)**		**P-value**
	Primary PCI group	**Fibrinolysis group**	
Anterior evolving MI			
No reperfusion, n=139	20	39	0.008
Incomplete reperfusion, n=107	32	26	0.67
Inferior evolving MI			
No reperfusion, n=21	36	0	0.04
Incomplete reperfusion, n=68	21	32	0.31

ECG, electrocardiogram; PCI, percutaneous coronary intervention; MI, myocardial infarction.

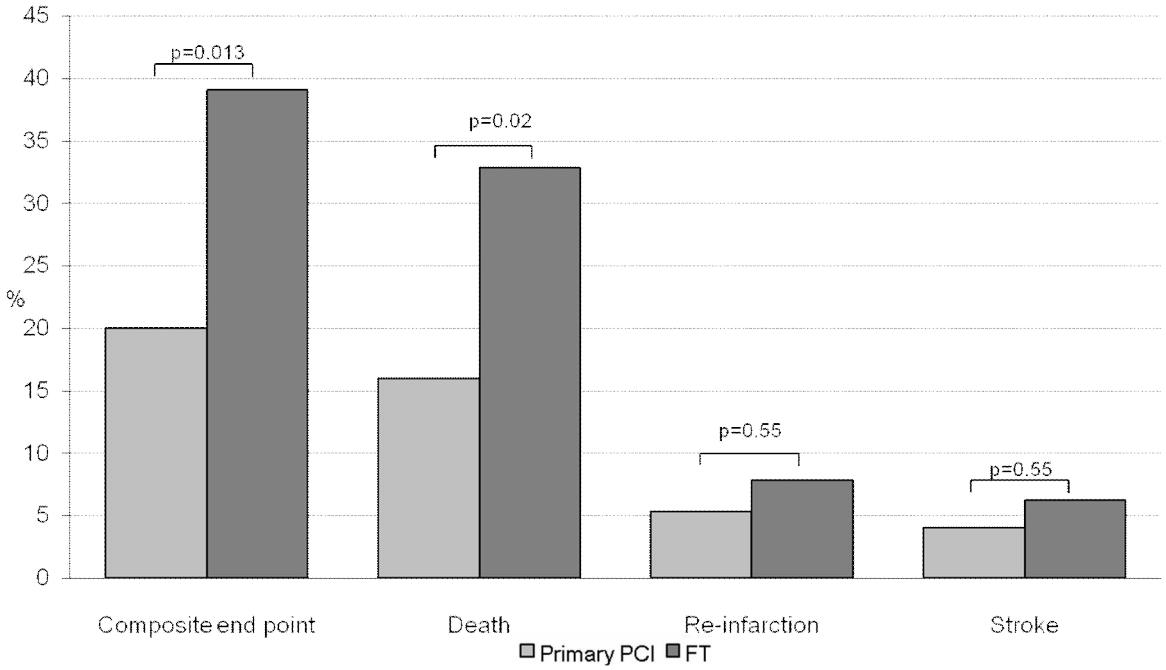


Figure 13. Composite and component end-points at 2.7-year follow-up in patients with the ECG pattern of anterior evolving myocardial infarction with no signs of reperfusion who were randomized to primary percutaneous coronary intervention (PCI) or fibrinolytic therapy (FT).

DISCUSSION

1. General considerations

ST-segment deviation from the isoelectric line was measured at different time-points, either at 80 ms after the J point (**I-II**) or at the J point (**III-IV**). Moreover, the isoelectric line was determined by drawing a line across the subsequent PQ segment (**I-II**) or the TP segment (**III-IV**). Computerized ECG analysis was used in studies **I-II** and the results of the present study pertain only to the Marquette 12SL system. Whether they would be different with other algorithms is open to speculation. The Marquette data matrix does not allow measurement at J+80ms; hence the computer selected a displacement at the midpoint of the ST segment (Elko and Rowlandson 1992). Clinically unacceptable limits of agreement comparing measurements of ST-segment deviations between a cardiologist experienced in ECG interpretation and the computer were mainly caused by the different measurement points. According to the present findings comparisons between cardiologist and computer-based measurements of J-point and T-wave deflections were considered to be within the limits of agreement in Bland-Altman analysis.

The number of patients fulfilling criteria for LAD-related coronary occlusion was small (**II**). This work thus represents a preliminary feasibility study to establish the value of the computerized ECG program to identify proximal LAD lesions. ECG was used as the golden standard to predict the culprit artery. Including coronary angiography findings in statistical analyses might have given additional information. An angiogram was taken in only 69 cases during hospital stay. Six patients had ECG findings indicating a proximal culprit lesion. Of these, 3 had a proximal culprit lesion in the coronary angiogram, but IRA could not be defined in 3 due to the long delay from admission to the angiogram. Also, cases with ECG confounders such as LBBB were excluded by manual interpretation. The power of the computer program to identify these ECGs was not tested.

Introducing markers of vessel size and more detailed angiographic information regarding the lesion in respect to septal and diagonal side branches could have improved the results of statistical analysis concerning the level of occlusion in the LAD determined by the ECG (**III**). It must be appreciated, however, that the coronary anatomy shows considerable variations between individuals. Excluding patients with multivessel disease and well-developed coronary collateral

circulation could have improved the results, but at the same time weakened their applicability to everyday clinical practice.

Data on TIMI perfusion grade would have improved the strength of the comparison between ECG changes and possible pathophysiologic mechanisms (**IV**). The definition of Q waves used here did not distinguish between reperfusion- and necrosis-related Q waves (**IV**). Although there was no difference in composite end-points according to the presence (76%) or absence of Q waves (24%) on the ECG in the evolving MI group as a whole, it is possible that patients with necrosis-related Q waves may have a less favourable prognosis compared with those with reperfusion-related Q waves. On the other hand, there are no well-established criteria to differentiate reperfusion- from necrosis-related Q waves.

Patients with ECG signs of pure lateral STEMI were excluded from the study (**IV**). However, the number of such STEMIs was low, 23 out of 1522. This is partly a consequence of the criteria for inclusion in the DANAMI-2 trial: to be randomized, a patient had to have cumulated ST elevation ≥4 mm (≥2 mm in at least 2 of leads I, aVL, V_1-V_6 or ST elevation ≥1 mm in all 4 leads II, III, V_5-V_6 or ST elevation ≥2 mm in at least 2 of leads II, III, V_5-V_6). In cases with pure lateral STEMIs massive ST deviation is seldom present (≥2 mm ST elevation in at least 2 of leads I, aVL, V_5-V_6). In cases with ST elevation ≥1 mm in all 4 leads II, III, V_5-V_6 the localization of the STEMI was classified as an inferior MI.

The present series was not originally planned as part of the DANAMI-2 study (**III, IV**). As the ECG investigators were totally blinded to patients' clinical data and angiographic findings and the number of patients was fairly large, the post hoc nature of the study should not have any significant impact on the results.

2. Computerized ECG analysis

2.1 Inter-observer variability

In the present study, inter-observer agreement between the two cardiologists was very good regarding determination of ST-segment elevation ≥2 mm in leads V_2, V_3 and ≥1 mm in lead III (κ=0.94, 0.93 and 0.80, respectively) as well as ST-segment depression ≥0.5 mm in lead III

(κ=0.86). It has been reported that inter-rater agreement tends to be better for interpretative compared with measured criteria, inter-observer agreement being very good (κ=0.89) in comparing interpretative criteria (physician's interpretation of the ECG based on both measured and subjective opinion that the changes represent acute transmural injury) as against good (κ=0.78) with measured criteria (physician's measurement of ST-segment deviation) (Massel et al. 2000). Our results demonstrated that inter-rater agreement could also be very good with measured criteria.

In summary, a high degree of inter-observer reliability is possible even with manual measurements of 12-lead ECGs demonstrating ST-segment deviation.

2.2 Selecting patients for fibrinolytic therapy in STEMI

The present findings indicate that automatically measured ST-segment deviations are smaller than those manually measured. Contrary to these results, Pelter and colleagues (1997) reported that measurements with a different computer were consistently and significantly higher than human measurements. In the study in question, all 12-lead ECG data were collected using the Mortara ELI 100 ST Monitor (Mortara Instrument, Milwaukee, WI), which uses the PR segment as the isoelectric reference point and was configured to measure ST-segment deviation at the J point plus 80 ms. The manual ST segment was also measured at 80 ms after the J point, but magnification was not used. In the present case there were different measurement points between manual and computerized analysis, which may constitute one explanation for the conflicting results. The patient populations were also different; in the study by Pelter's group (1997) all ECGs were recorded during the balloon dilatation of the coronary artery, whereas the present study included all consecutive patients for suspected ACS with or without ST-segment deflection. In both studies the ST segment was rounded to the nearest 0.5 mm. Computer analysis for ST elevation uses exact thresholds, whereas human interpreters usually draw a subjective conclusion as to whether the ST changes represent acute ischemia or not. Humans are more likely to round down when measuring ST-segment deviation, erring thus more conservatively. Especially in the study by Pelter and colleagues (1997), a subjective tendency to round down to the nearest 0.5 mm, leading systemically to underestimation of ST elevation, is probable because the investigators did not use the aid of a hand-held magnifying lens.

Magnification, as was used in the present study, helps to measure ST-segment deviation more precisely.

In looking for optimal cut-off values for significant ST-segment deviations, our aim was to avoid a clinical scenario where reperfusion therapy would cause complications in patients without coronary occlusion. Hence we decided to keep the specificity close to 100% to avoid false-positive cases. Automated ECG analysis has already been used in decision-making on FT (Lamfers et al. 2004). Nonetheless, using strict ECG criteria would lead to overuse and commercial automated analysis to underuse of FT (Massel et al. 2000). The computer algorithm underestimated the proportion of potentially fibrinolysis-eligible AMI. Strict reliance on computerized interpretation with the Marquette 12SL system alone would have led to underuse of FT compared with interpretive opinion (21.3 vs. 34.6%, $p<0.005$) (Massel et al. 2000). In the light of the present findings, the optimal cut-off point was 1.15 mm for the computer program tested to detect true ST-segment elevations ≥2 mm when using interpretation of an electrocardiographer as gold standard. The corresponding value was 0.45 mm for an actual ST elevation ≥1 mm and 0.35 mm for an actual ST elevation ≥0.5 mm. These cut-off points were used in order to maintain the specificity at 98 % or more concomitant with an acceptable sensitivity. In the above-mentioned study by Massel and associates (2000), the Marquette 12SL algorithm had a specificity of 100% and a sensitivity of 61.5%. Elko and Rowlandson (1992) reported that computerized interpretation of anterior AMI has a sensitivity of 79 % and a specificity of 93 % when the Marquette 12SL program measures ST deviation at the end of the ST segment and a sensitivity of a 75 % and a specificity of 91 % when it measures at the midpoint of the ST segment. According to the present findings, these midpoint results would be better if correction for difference is made. However, the best agreement could be achieved if the ST elevation is measured at the J point. The findings here emphasize the importance of using an expert electrocardiographer's ECG interpretations as gold standard when analyzing computerized measurements or introducing new computer-based diagnostic tools in clinical situations.

In summary, reliance on computerized ECG interpretation would lead to inappropriate use of FT in situations in which qualifying ECG criteria are actually met. The sensitivity of computerized ECG interpretation apparently remains low, at about 50 to 80%, and hence many candidates potentially eligible for reperfusion therapy might be missed. In the future, artificial neural networks might improve the usefulness of computerized ECG analysis in selecting patients for reperfusion therapy. One of the principal findings in the present study was that the

accuracy of computerized measurement of ST elevation is insufficient and that precise cut-off points should be used in commercial automated analysis algorithms for optimal clinical decision-making.

3. Predictive accuracy of the ECG

3.1 LAD as the infarct-related artery

To the author's knowledge the present work (**III, IV**) is the first large-scale prospective study to compare 12-lead ECG with coronary angiography findings from the acute phase and with clinical outcome. The results represent the diagnostic information from one single 12-lead ECG without data on past cardiovascular history such as cardiomyopathies, prior MI, previous ECG findings or the clinical condition of the patients. In this study, a culprit lesion in the LAD could be reliably predicted with a sensitivity of 87% and a specificity of 96% in a large cohort of STEMI patients even when patients with known ECG confounders such as pathological Q waves and those with multivessel disease were included. Also the positive and negative predictive values were high, 95% and 88%, respectively.

This study (**II**) represents the first attempt to compare computer-based with manual ECG interpretation in arriving at an anatomical ECG interpretation. The hypothesis was that it is possible to construct a computer ECG analysis program which has a good correlation with manual interpretation of the ECG for recognition of patients with occluded LAD. The study population comprised the whole spectrum of ACS patients. We used cut-off points for significant ST-segment deviations ($\geq$2, $\geq$1 and $\geq$0.5 mm). These ST deviations are the most critical in the algorithm for anatomical interpretation. We compared computerized interpretations between uncorrected (expressed in the data matrix) and corrected measurements (cut-off points). The computer program was able to detect LAD-related STEMI with high specificity (99%) when using manual interpretation as gold standard. The use of ST-segment corrections improved the sensitivity to detect an occlusion in the LAD (a sensitivity of 58 % with uncorrected and 67 % with corrected computer program). The agreement between the manual analysis and the uncorrected or corrected computer program in the determination of the LAD as an IRA was good (κ=0.65 and κ=0.71, respectively).

In summary, the ECG is reliable in identifying the LAD as the IRA even in cases with ECG confounders (**III**). A computerized ECG program can recognize an occlusion of the LAD with good sensitivity and specificity in patients with ACS (**II**).

3.2 Level of occlusion in the LAD

A number of rather small retrospective studies have been published comparing different ECG patterns with coronary anatomy to predict culprit arteries and the level of occlusion (Birnbaum et al. 1994, Tamura et al. 1995, Engelen et al. 1999, Koju et al. 2003, Vasudevan et al. 2004) (Table 5 [Page 34]). Most of these previous studies have excluded patients with multivessel disease, although this situation is often encountered in daily clinical practice (Andersen et al. 2003b). There is also a common problem with timing; the "golden standard", coronary angiography, has been performed up to two weeks after FT in the above-mentioned studies. The site of the most severe coronary narrowing does not necessarily reflect the size and location of the ischemic bed. In many cases the plaque ruptures at a bifurcation site. The thrombus occluding the stem of the coronary artery may progress proximally and/or distally, so that during acute ischemia one or more of its side branches could have been occluded and subsequently, after (partial) dissolution of the clot, the side branches may appear patent. It may be difficult to assess whether the thrombotic process has extended more proximally (e.g. covering a side branch) in the acute phase when the angiography is performed later in the disease process. Moreover, coronary angiography is not sensitive to depict small collateral vessels which may (at least partially) nourish the segments assumed to be supplied by the IRA. It has been speculated, that even visible collaterals may disappear shortly after re-canalization of the IRA. Optimally both ECG recording and coronary angiography should be performed in close temporal proximity and during the acute phase of the MI process, as was done in the present study (**III, IV**).

Consistent with the present findings, ST elevation in lead aVL (and usually also in lead I) in proximal LAD occlusion has been related to the first diagonal side branch, supplying the anterolateral wall, this being occluded by the thrombotic process (Tamura et al. 1995, Engelen et al. 1999, Arbane and Goy 2000). The injury vector in anterolateral MIs is directed to the left shoulder, towards leads I and aVL. Our finding of a PPV of 84% and an NPV of 45% for ST elevation ≥0.5 mm in lead aVL as a marker of proximal LAD occlusion is similar to that in a

prospective study by Arbane and Goy (2000) (PPV 81%, NPV 57%), where the angiogram was also performed within a few hours of onset of symptoms. However, the sensitivity of 82% and specificity of 50% reported in the present study differ from the results of that study (sensitivity 58%, specificity 81%). The investigators measured the ST-segment elevation ≥1 mm in lead aVL 80 ms after the J point, whereas in the present study an elevation of 0.5 mm at J point was used. It is to be presumed that different ST segment criteria constitute the reason for the higher specificity observed in the study by Arbane and Goy (2000) and the higher sensitivity reported here. When there is no opposite injury vector in the inferior segment, higher ST elevation is present in the ECG leads representing the anterolateral segment of the LV. This absence of attenuation explains how ≥1 mm ST elevation in lead aVL is a specific but insensitive marker of the proximal LAD occlusion. Kim and associates (1999) reported high, 91%, sensitivity and 90% specificity of an ST injury pattern in aVL if any of the following criteria were met: first, ST elevation ≥0.5 mm; second, any lesser degree of ST elevation if associated with symmetrical T-wave inversion; third, any isoelectric ST segment associated with both symmetrical T-wave inversion and an abnormal Q wave, in predicting a culprit lesion prior to the first diagonal branch. The study in question, however, also included patients in later stages of the infarct process (EMI) than in the present study (only patients with PIS were included). Another limitation of the afore-mentioned study was the late timing of coronary angiography, on average 6.3 days after the initial ECG. A group under Koju (2003) showed in a rather small patient cohort excluding patients with organic heart disease and previous MI that ≥0.5 mm ST elevation in lead aVL or aVR was of value in predicting a proximal LAD lesion (sensitivity 73 and 42%, respectively and specificity 78 and 97%, respectively). In that study angiography was performed within two weeks from the acute phase.

We found that adding any ST elevation in lead aVR to the definition of a proximal occlusion of the LAD irrespective of changes in other extremity leads improved the sensitivity of the ECG analysis compared to using only ST elevation in lead aVL (sensitivity 87 vs. 82%, respectively). Engelen and colleagues (1999) showed that ST elevation in lead aVR was a specific sign of a proximal LAD occlusion before the first septal branch. However, the sensitivity of their ECG finding was low. The authors speculated that transmural ischemia of the basal septum with an injury current directed to the right shoulder would explain the ECG finding. Alternatively, the ECG finding could manifest the pathophysiologic consequences of extensive ischemia in the whole anterior wall, the major part of the ventricular septum and significant parts of the anterolateral wall, induced by a very proximal LAD occlusion. In patients

with NSTEMI ST-segment elevation in lead aVR in addition to widespread ST depression indicates 3-vessel or left main coronary artery disease (Gorgels et al. 1993, Nikus et al. 2004). In these cases extensive subendocardial ischemia induced by severely elevated left ventricular end-diastolic pressure and diastolic dysfunction has been proposed. Kosuge and associates (2001) reported that the proximity of the culprit lesion in the LAD was similar in patients with ST elevation, without ST-segment deviation or with ST depression in aVR. However, they only included patients with ST elevation ≥2 mm in >2 contiguous precordial leads and ST elevation ≥1 mm in leads I, aVL possibly resulting in a selection bias favoring the ECG pattern of proximal LAD occlusion.

In the present study, the strongest correlation with coronary angiography findings showing proximal LAD occlusion was found when its proximal occlusion electrocardiographically was defined as either ≥0.5 mm ST elevation in lead aVL or any ST elevation in aVR and when patients with 1 mm or more ST elevation in all inferior leads were excluded from the analysis (sensitivity 94%, specificity 49%, PPV 85% and NPV 72%). A minority of patients with LAD occlusion showed simultaneous ST elevation in the precordial and the inferior leads II, III and aVF (Sadanandan et al. 2003). Autopsy reports have shown that in the majority of patients the LAD wraps around the LV apex and extends up the posterior interventricular sulcus to a variable degree (James 1960). Some studies have shown that the proportion of cases with a large LAD wrapping around the apex is significantly higher among anterior MI patients with simultaneous inferior ST elevation, and conversely, significantly lower in those with ST depression observed in the inferior leads (Sasaki et al. 2001, Martinez-Dolz et al. 2002). Sasaki and colleagues (2001) have shown that, indeed, proximal occlusion of a short LAD causes ST elevation in leads I and aVL. However, proximal occlusion of a long LAD which wraps around the cardiac apex is not often associated with ST elevation in lead I and aVL or reciprocal ST depression in the inferior leads. The proximal occlusion of a wrapping LAD produces concomitant injury to two electrically opposite areas, the inferior and anterolateral wall of the LV. This in turn may attenuate the ST elevations in the electrically opposite anterolateral leads (I, aVL) and inferior leads (II, III, aVF), resulting in an isoelectric or even depressed ST segment in lead aVL despite a proximal LAD occlusion. Our finding that ST elevation in lead aVL is a more sensitive marker of proximal LAD occlusion if patients with inferior ST elevation are excluded from the analysis supports the findings of Birnbaum and associates (1993c) that ST elevation in lead aVL is not a reliable sign of a proximal lesion in the LAD in cases with ST elevation in all inferior leads.

Hence, the size of the artery should be added as a variable when defining the level of occlusion in the LAD.

The present study adds to the current knowledge that a computer program can recognize an occlusion of the proximal LAD in patients with ACS. The use of ST segment corrections also improved the ability to determine the level of the LAD occlusion. The sensitivity and specificity of the uncorrected and corrected computer program to detect proximal occlusion in the LAD were similar (sensitivity 86% and specificity 100% in both analyses). However, the correlation between the manual and the uncorrected vs. corrected computer program in defining the site of a proximal occlusion in the LAD was better with the corrected than uncorrected ST segment cut-off points (κ=0.72 vs. κ=0.65, respectively). The corrected computer program was more sensitive to detect distal occlusions in the LAD than the uncorrected program (sensitivity 40 vs. 20%, respectively), while there was no difference in specificity (99% in both analyses). An electrocardiographer and the corrected computer program interpreted the ECG finding of distal occlusion in the LAD with good agreement (κ=0.72). In reality, the capability of computer-assisted anatomic ECG interpretation to find proximal LAD lesions is poorer. In our series (**II**), the ECG criteria for proximal LAD lesion were not tested against coronary angiography.

In summary, the site of occlusion in the LAD could be reliably predicted by 12-lead ECG in patients with acute anterior STEMI. The presence of ST elevation ≥0.5 mm either in lead aVL or any ST elevation in aVR in association with precordial ST-segment elevation in at least two contiguous leads (including V_2, V_3 or V_4) is an ECG marker with good sensitivity, and positive and negative predictive values for a culprit lesion proximal to a medium-sized or large diagonal side branch. Computerized anatomical interpretation of the ECG is feasible and allows detection of a proximal LAD occlusion with good accuracy. The presence of ST-segment elevation in all inferior leads makes it unreliable in predicting the level of occlusion in patients with acute anterior wall MI.

4. Prognostic significance of lesion location

The present paper reports that anterior MI provided independent prognostic information in multivariable analysis. This finding is congruent with those in earlier studies both from the FT and the primary PCI era (Thanavaro et al. 1982, Stone et al. 1988, Boersma and The Primary Coronary Angioplasty vs. Thrombolysis Group 2006).

The results of the present and previous studies concerning the prognostic significance of proximity of the culprit lesion in the LAD are conflicting. In the present case proximal LAD-related MI was not associated with poorer clinical outcome at 30 day or 2.7-year follow-up than LAD-related MI caused by distal occlusions in patients treated with either primary PCI or FT. This was true both for ECG- and angiographically defined proximal LAD disease. Karha and associates (2003) found that proximal lesion in the LAD was associated with a higher incidence of in-hospital death or recurrent AMI compared with mid or distal lesions in patients with AMI. They used pooled data from four different trials comparing different pharmacological reperfusion therapies, and angiographic data were obtained 90 minutes after fibrinolytic administration. One possible explanation for the different results compared to our study could be the difficulty in identifying the exact culprit lesion after reperfusion therapy. The authors in question considered a culprit lesion as proximal if it was located before the first LD branch and mid if located between the first and the second LD branch. All lesions distal to the second LD branch were considered distal. In contrast to our approach, their definition did not take into account the size of the side branch. Probably, small side branches are without major electrophysiologic or clinical importance. Accordingly, the definition used in that study could classify a culprit lesion distal to a minor first diagonal side branch as a mid-LAD occlusion, although the lesion was situated quite proximally in the artery with a large area of myocardium at risk. This highlights the difficulties often encountered when defining the level of occlusion in different individuals with wide variations in coronary anatomy.

Elsman and colleagues (2006) reported that proximal LAD-related infarcts treated with primary PCI were associated with higher short- and long-term mortality compared with distal LAD lesions. In their single-center study from the mid-1990s, the use of antithrombotic therapy differed significantly from that in more recent trials such as the DANAMI-2. They also did not report ischemic time between onset of symptoms and first balloon inflation. In our study patients with acute STEMI early after the onset of symptoms were included. We would hypothesize that the more complete and durable reperfusion offered by PCI in the DANAMI-2 trial, and the aggressive contemporary medical therapy used in secondary prevention, neutralized the negative prognostic effect of the proximality of the culprit lesion in LAD within the primary PCI treatment arm. Perhaps more surprisingly, there was no difference in clinical outcome in the fibrinolysis treatment group between proximal and distal occlusion as defined by ECG. Consistent with the present findings it was reported from the CADILLAC trial that in comparing outcomes among patients with LAD-related infarction relative to the location of the culprit

lesion, one-year survival was similar among those with an ostial/proximal location vs. a mid/distal location (8.9 vs 6.6%, p=0.52) (Kandzari et al. 2006). In the CADILLAC trial as in the DANAMI-2 trial, the antithrombotic therapy was modern and well implemented.

In summary, the location of AMI has an influence on prognosis. Patients with anterior STEMI have a higher rate of a composite end-point of death, re-infarction or disabling stroke at 2.7 years' follow-up compared with those with non-anterior infarction. However, the prognostic significance of the level of occlusion in the LAD in the modern era of acute STEMI treatment should be reassessed.

5. Major findings of the study

5.1 Duration of ischemia

Time is myocardium, the familiar adage in the cardiovascular community, is central to the controversy over the best modality for reperfusion after AMI. Acute treatment strategy and subsequently prognosis are influenced by the duration of ischemia in patients with acute STEMI. However, the duration of ischemia may be difficult to access by patient history (historical timing) alone. Patients often do not recall the precise time point of symptom onset, especially when symptoms are atypical or intermittent due to the alteration of occlusion and opening of the IRA in cases with unstable plaque ruptures. This is a noteworthy issue in that this type of historical data is a key criterion for many treatment protocols. As described by Sclarovsky (1999a, 1999b, 1999c), dynamic ECG changes reveal what is happening in the myocardium during the infarct process irrespective of historical timing.

In the present study, patients with EMI had about 1 hour longer estimated median time delay from symptom onset to randomization and to reperfusion therapy compared to those with PIS, indicating a later stage of the evolving MI process. The finding here was that time to treatment >4 hours was not an independent predictor of outcome when the ECG pattern indicating the stage of the infarct process was included in the model. Interestingly, neither was PCI independently predictive. However, in multivariable analysis the ECG finding of EMI indicated a poor prognosis (increased incidence of the combined end-point of death, re-infarction and disabling stroke) compared to the ECG finding of PIS at 2.7-year follow-up (HR 1.524, CI

1.009-2.299, p=0.045). The interaction term indicated that the ECG pattern was independently predictive. In view of the limitations attending patient-reported timing of symptom onset, ECG phasing and acuteness scores were developed, and later modified, by Anderson and Wilkins to estimate the extent to which a patient has progressed through the MI process by the time of clinical presentation (Wilkins et al. 1995, Corey et al. 1999). The clinical significance of the Anderson-Wilkins (AW) score has been validated, and the ECG method (AW score) has been reported to be superior to historical timing in predicting myocardial salvage and prognosis after reperfusion therapy (Sejersten et al. 2007). However, to be clinically useful, the acuteness score should be an integral component of a commercial automated ECG analysis program (Ripa et al. 2005). So far, such programs are not universally available.

Our results support an alternative approach using simple ECG patterns (PIS and EMI) to divide STEMI patients into clinically relevant categories. In fact, these patterns are distinguished by the same ECG parameters, the Q and T waves, as used in the AW scoring system. The conflicting results in previous studies concerning the benefit of primary PCI treatment at different time-points after symptom onset (Steg et al. 2003, Widimsky et al. 2003, Busk et al. 2007) may be explained by the unreliability of data of historical timing and mainly by the fact that in previous studies more comprehensive ECG analysis was not utilized in defining the stage of the infarct process. Randomized studies of acute STEMI use cut-off points for the amount of ST elevation for patient inclusion (Keeley et al. 2003). Changes in the Q and T waves are not considered. According to our results, clinically important information regarding the pathophysiology and the timing of the ischemic process may be contained in these ECG parameters. It is justified to suggest that the PIS and the EMI ECG patterns certainly need to be taken into account when designing the protocol for new trials of reperfusion therapy in STEMI.

In summary, time from the onset of symptoms related to MI to randomization and time to first balloon inflation was >1 hour longer in patients with EMI compared to those with PIS. The ECG pattern indicating the stage of the infarct process is independently predictive for outcome, whereas PCI treatment or time to treatment >4 hours is not. Based on these findings one may presume that the dynamic ECG changes are precise and clinically valuable tools in assessing the time course of ischemia in the myocardium.

5.2 Risk stratification

5.2.1 TIMI risk score

From previous studies one might conclude that reperfusion strategy should be selected mainly based on time delays, namely the presentation delay (which should be less than 12 hours) and the PCI-related delay (which should be less than 1 or perhaps 2 hours). However, it has previously been proposed that in selecting a reperfusion treatment strategy, not only time delays but also the baseline characteristics of patients presenting with an acute STEMI should be taken into account (Thune et al. 2005, Pinto et al. 2006). The findings of the present study are consistent with previous results. Pinto and associates (2006) reported in their real-life data from the large NMRI registry that patient age, duration of symptoms and infarct location significantly modulated how rapidly the survival advantage of primary PCI compared to FT therapy was lost. We also found that anterior STEMI and age are independently indicative of poor prognosis. In addition, we found that low body weight is associated with worse outcome. The TIMI risk score is the key tool in the kind of risk stratification proposed by other investigators. However, although the TIMI risk score is well validated it is somewhat impractical. Decisions on treatment strategy are often made on an emergency basis, also in consultation by paramedics attending the patient. It may not be feasible in the acute clinical setting to check all twelve variables needed for scoring, considering that patients with acute STEMI are often in pain and not necessarily adequately cooperative. In this kind of situation it is important to identify high-risk patients without any delay. More rapidly available and simple tools than the TIMI risk score for identification of high-risk patients are needed, and an expanded role for the ECG in risk stratification has been studied in this present work.

In summary, the problem of the TIMI risk score is its complexity in rapid decision-making.

5.2.2 Different ECG parameters

When using only traditional ECG parameters, typically ST-segment elevation, patient outcome in the DANAMI-2 trial in different subgroups has favored primary PCI. Regardless of infarct location invasive therapy has been superior to non-invasive (Andersen et al. 2003b). When

comparing the prognostic value of the sum of ST-segment elevations within quartiles the lower composite end-point rate for primary PCI compared with FT was observed only in the fourth ΣST quartile (Sejersten et al. 2006). All studies comparing the sum of absolute ST-segment deviation have been based on the hypothesis that each lead represents the same amount of myocardium and that a similar size of ischemic area in different locations of the LV will result in a similar magnitude of ST deviation in the same number of leads. However, the 12-lead ECG does not equally represent all myocardial regions and, moreover, ischemia in opposed regions may attenuate or augment ST deviation. To be useful in clinical practice, the reproducibility of any scores or quartiles should be verified in large cohorts of patients, and they should form an integral component in commercial automated ECG analysis programs. Further, factors such as width of the chest wall, the distance of the electrode from the ischemic zone, the myocardial mass and presence of ischemic preconditioning and collateral circulation have a major influence on the absolute magnitude of ST deviation and should hence be taken into account.

It has recently been shown that defining GI on the presenting ECG in the DANAMI-2 study cohort enabled the identification of high-risk patient populations with adverse outcome (Sejersten et al. 2006). This, together with the results of the present study, indicates that extension of ECG interpretation beyond traditional ST segment analysis is important. Interestingly, Sejersten and colleagues (2006) reported that the time from symptom onset to treatment was equal in both groups (GI 2 and GI 3). This reveals that, contrary to the ECG pattern of PIS and EMI, the severity of the ischemia/infarct process, as classified using GI groups derived from admission ECGs, is not time-dependent. Defining the GI from the ECG is generally easy and might prove useful e.g. when one has to decide on priority for primary PCI between two patients with an otherwise similar risk profile (e.g. PIS pattern on the ECG, same age, same infarct location and same bleeding risk).

In summary, the sum of ST-segment elevations is not practical in clinical decision-making, whereas defining GI may give valuable information in risk stratification.

5.2.3 Significance of the Q wave

The role of Q waves in the acute phase of STEMI is rather poorly established. Classically, the appearance of Q waves has been associated with irreversible myocardial necrosis. However, it has been shown that the early appearance of Q waves may indicate reperfusion in the ischemic myocardium and is not a sign of irreversible myocardial damage. Also, the Q waves in the acute

phase of STEMI may be transient (Gross et al. 1964, Blumenthal et al. 1975, Bateman et al. 1983, Bar et al. 1987, Rechavia et al. 1992, Raitt et al. 1995). On the other hand, in a recent HERO-2 substudy the presence of Q waves in the initial ECG was an independent predictor of higher 30-day mortality in patients treated with FT (Wong et al. 2006). In our series, EMI (Q waves present in ¾) was associated with worse prognosis compared to PIS. In the EMI group as a whole there was no difference in composite end-points according to the presence or absence of Q waves on the ECG. In the anterior EMI group without ECG signs of reperfusion, primary PCI resulted in a dramatic 51% reduction in the relative risk of composite end-point. Accordingly, patients with anterior STEMI presenting with a combination of Q waves, ST elevation and positive T waves in the anterior leads should have high priority for invasive therapy. This conception is in accord with the pathophysiologic message from the ECG in these cases – a high probability of an occluded IRA (ST elevation with positive T waves), with an extensive area of jeopardized myocardium (anterior localization).

In summary, the early appearance of Q wave in patients with acute STEMI is not a marker of a "lost case" for reperfusion therapy.

5.2.4 Significance of the T wave

The predictive value of a negative T wave as a marker of reperfusion is not generally agreed. However, it has previously been shown that patients with acute anterior MI in whom ST-segment elevation and positive T waves persist at discharge from the coronary care unit have a higher probability of a non-patent LAD compared to those with an isoelectric ST segment with negative T waves (Atak et al. 2004). It has also been shown that the presence of a combination of isoelectric ST segment and negative T wave is related to normal (TIMI 3) epicardial flow, whereas an elevated ST segment and positive T wave indicates impaired coronary flow (Kusniec et al. 1997). Early inversion of the T wave in the leads showing ST elevation have been associated with improved outcome related to an open IRA, restored myocardial blood flow, reappearance of the R wave and better left ventricular function after AMI (Doevendans et al. 1995, Agetsuma et al. 1996, Porter et al. 2000, Sgarbossa et al. 2000).

Although our patients with EMI had ~4 h median time delay to reperfusion therapy, those with inverted T waves showed no significant difference in outcome between mechanical and pharmacological therapy. This may seem contradictory, as the effect of FT is significantly reduced after 3 h delay from symptom onset to treatment (Fibrinolytic therapy trialists' (FTT)

collaborative group 1994). Also in randomized trials such as PRAGUE-2 and CAPTIM, the superiority of primary PCI relative to fibrinolysis was most evident after 2-3 h delay from symptom onset (Steg et al. 2003, Widimsky et al. 2003). Acknowledgement of negative T waves in this context as markers of restored epicardial and myocardial blood flow could explain this finding. Some studies have shown that the occurrence of reperfusion before PCI is associated with more favorable clinical outcome (Brodie et al. 2000). The therapeutic advantages of primary PCI might be less obvious in cases with an open IRA. High-risk patients such as those with a large thrombus burden and increased risk of distal embolization with no-reflow may outweigh some of the benefits from PCI (Singh et al. 2001, Cafri et al. 2004). The findings of the present study support the afore-mentioned speculations. There were no significant differences between reperfusion therapies in EMI patients, with the exception of patients with anterior infarcts and no evidence of reperfusion (i.e. absence of negative or biphasic T waves) who demonstrated benefit with primary PCI.

In summary, during the infarct process, T-wave inversions in the leads with concomitant ST elevations indicate incipient reperfusion, containing clinically valuable information when selecting optimal reperfusion therapy for patients with STEMI.

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5.3 Impact of the present study on current treatment strategies

The main novelty value of this present study was in showing differences in treatment response to reperfusion therapy with different ECG presentations. It represents the first attempt to assess the clinical significance of two distinct ECG patterns, ST-segment elevation without (PIS) or with (EMI) pathological Q waves or negative T waves, in a large patient cohort. In cases of acute chest pain the PIS represents a window of opportunity to treat before irreversible myocardial damage develops. Such a conception is supported by the results presented here. A higher rate of the composite end-point of death, re-infarction and disabling stroke was observed in EMI vs. PIS patients at a median follow-up of 2.7 years (11.4 vs. 6.9% per 100 person-years, respectively, $p<0.001$). The difference was explained by the higher mortality in the EMI group. This is not entirely unexpected, since time delay to randomization and treatment was longer in EMI patients. We found that the PIS pattern (Figures 5B [Page 63] and 14A) was associated with a lower long-term overall event rate in patients treated with primary PCI compared with FT (5.5

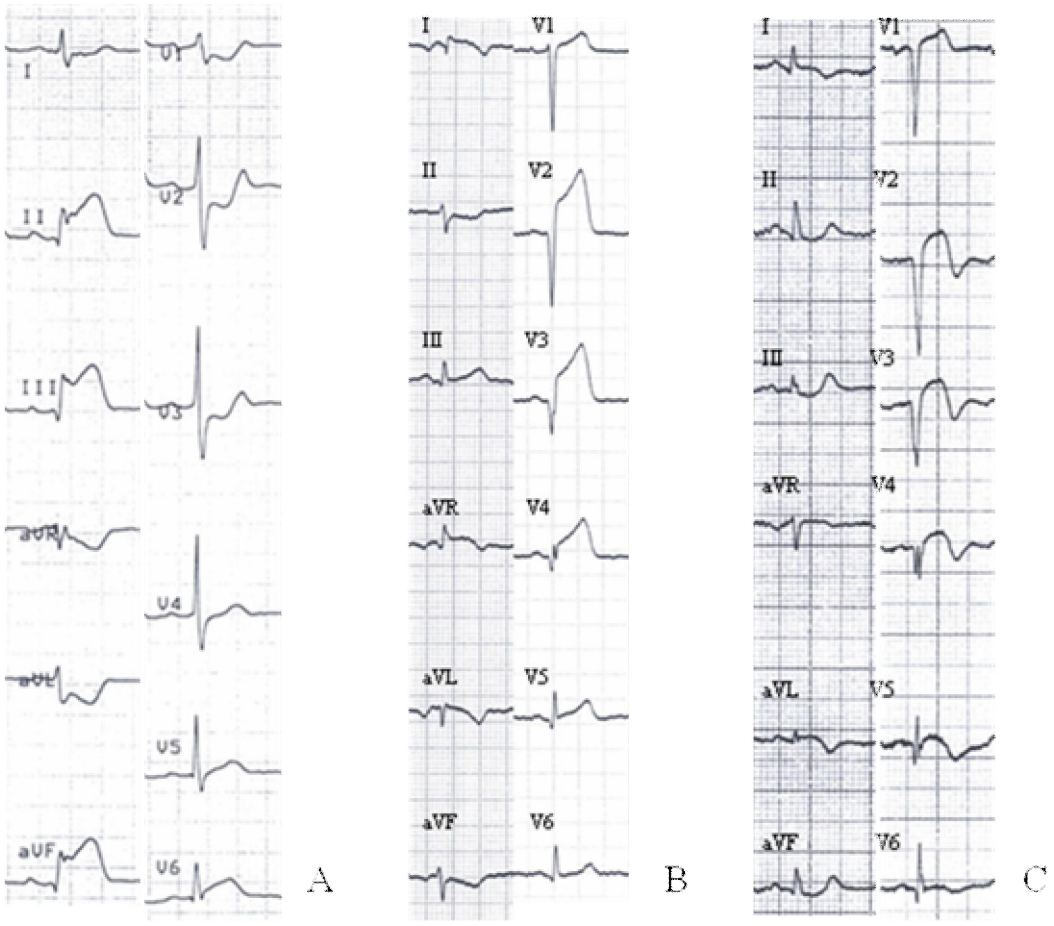

Figure 14. (A) As a sign of inferior pre-infarction syndrome, the ECG reveals ST-segment elevation in leads II, III, aVF, V_5 and V_6 with positive T waves. No pathological Q waves are present in the inferior leads. (B) Pathological Q waves are seen in the anterior leads V_2-V_4 with concomitant ST elevations, the T waves are positive. This is the ECG pattern of anterior evolving myocardial infarction (EMI) without signs of reperfusion. (C) Anterior EMI with signs of incomplete reperfusion is defined as ST elevation with inversion of the T wave. The terminal portion of the T wave is negative in leads V_2-V_6.

[4.4-6.9] and 8.5 [7.0-10.4] per 100 person-years, respectively, RR=0.6, p=0.004). The number needed to treat with primary PCI to avoid one end-point event during follow-up was 17. Also patients with anterior EMI without T-wave inversion (Figure 14B), an ECG sign of reperfusion, had better outcome with invasive therapy than with pharmacologic reperfusion. In these patients, the number needed to treat with primary PCI to avoid one death was 6 at 2.7-year follow-up. Maximal effort should be put into providing immediate invasive treatment for these patient groups.

In the present study, patients with inferior EMI without ECG signs of reperfusion had poorer outcome with PCI than with fibrinolysis. This may be only a trend in view of the small number of patients in this subgroup (n=21). Nonetheless, we cannot rule out harm caused by invasive therapy in relatively low-risk patients. Furthermore, the present findings add to the current knowledge that if T-wave inversion was present (Figure 14C), FT resulted in long-term outcome similar to that in primary PCI in both anterior and inferior STEMI. Especially when access to primary PCI is limited, FT could be a reasonable alternative in cases presenting with inferior EMI or anterior EMI with signs of reperfusion (negative or biphasic T wave), optimally followed by invasive evaluation within the next few hours.

The site of the culprit lesion in the LAD is predictable based on the ECG. However, the proximality of the occlusion in the LAD does not seem to have any major impact on prognosis in the modern era of STEMI treatment. This notwithstanding, from a practical point of view, the anatomic information yielded by the ECG is a most valuable tool in the catheterization laboratory to evaluate the target for PCI especially in patients with IRA patency and several stenoses.

In summary, it is possible to identify patients in whom every effort should be made to transfer for primary PCI based on the PIS and EMI ECG patterns. This observation warrants a re-thinking of information derived from ECG in acute STEMI. The PIS and EMI patterns should probably be incorporated in the risk assessment procedure in cases with STEMI and may be included in the randomization algorithms for clinical trials assessing treatment results and prognosis in STEMI.

SUMMARY AND CONCLUSIONS

In patients with STEMI, the primary objective is to restore the flow in the IRA. Reperfusion can be obtained by FT or primary PCI. There is still no consensus as to whether all patients benefit from an invasive strategy. Furthermore, especially during off-hours, most patients are treated in hospitals without 24h/7d cardiac catheterization facilities and inexperienced physicians on duty are in the front line of decision-making in acute STEMI. For clinicial use, it is of vital importance to have reliable criteria which identify high-risk patients in whom every effort should be made to transfer for primary PCI and low-risk patients in whom FT might be an alternative initial option. Ideally, such a diagnostic approach should be readily available and fast as with computer-assisted ECG interpretation added to the information gained from clinical variables.

The principal findings and conclusions are:

1. The accuracy of computerized measurement of ST elevation is insufficient compared with manual measurements and, for optimal clinical decision-making, precise cut-off points should be used in commercial automated ECG analysis algorithms.

2. The use of corrected ST segment cut-off values improves the results of automated ECG interpretation. A computer program can recognize an occlusion of the proximal LAD artery with good sensitivity and specificity in patients with ACS. Accordingly, the findings in the present study open up new opportunities for computerized analysis of the ECG.

3. The presence of ST elevation ≥0.5 mm either in lead aVL or any ST elevation in aVR in association with precordial ST-segment elevation in at least two contiguous leads (including V_2, V_3 or V_4) is an ECG marker with good sensitivity, and positive and negative predictive values for a culprit lesion in the LAD proximal to a medium-sized or large LD side branch. Patients with a proximal lesion in the LAD artery had a clinical outcome at 30 days and 2.7-year follow-up similar to that of patients with a lesion located more distally in the LAD. The presence of ST-segment elevation in all inferior leads

makes it unreliable to predict the level of obstruction from the ECG in patients with acute anterior wall STEMI.

4. The information obtained from more detailed ECG analysis, also involving Q and T wave morphology, is useful in selecting reperfusion therapy for a patient with acute STEMI.

5. Patients with acute anterior or inferior STEMI without Q waves and with positive T waves (PIS), and those with anterior AMI with Q waves, ST elevation and positive T waves (anterior EMI without signs of reperfusion) have better long-term outcome with primary PCI than with FT. If T wave inversion is present, FT results in long-term outcome similar to that with primary PCI both in anterior and inferior STEMI.

In the light of the evidence obtained from the present study, it may be concluded that the first-line ECG interpreter has a key role in selecting optimal reperfusion therapy for patients with acute STEMI. The key tool is to hand; the ECG recorded in the acute phase. Based on the findings in this thesis, an expanded role for the PIS and EMI ECG patterns in risk stratification in STEMI is proposed.

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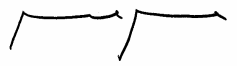

Markku Eskola

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ORIGINAL COMMUNICATIONS

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Comparative Accuracy of Manual Versus Computerized Electrocardiographic Measurement of J-, ST- and T-Wave Deviations in Patients With Acute Coronary Syndrome

Markku J. Eskola, MD[a,*], Kjell C. Nikus, MD[a], Liisa-Maria Voipio-Pulkki, MD, PhD[c], Heini Huhtala, MSc[d], Tiina Parviainen, MSc[b], Juha Lund, MD[e], Tuomo Ilva, MD[e], and Pekka Porela, MD, PhD[e]

Accurate and rapid electrocardiographic interpretation is of crucial importance in acute coronary syndrome (ACS). Computerized electrocardiographic algorithms are often used in out-of-hospital settings. Their accuracy should be carefully validated in ACS, particularly in ST-elevation myocardial infarction. This study evaluated the comparative accuracy of lead-specific computer-based versus manual measurements of the J-point, ST-segment, and T-wave deviations in standard 12-lead electrocardiograms (ECGs) (excluding lead aVR). Sixty-nine consecutive patients with suspected ACS were included. The interobserver reliability in the determination of ST-segment deviation ≥0.2 mV in leads V_2 and V_3 was very good ($\kappa = 0.94$ and 0.93, respectively). Agreement between a cardiologist and the computer regarding ST elevation ≥0.2 mV in lead V_2 was moderate ($\kappa = 0.72$) and in V_3 was very good ($\kappa = 0.85$). For ST depression or elevation ≥0.05 mV in lead LIII, agreement was good and moderate ($\kappa = 0.79$ and 0.51, respectively). Bland-Altman analysis demonstrated clinically acceptable limits of agreement comparing measurements of the J point and the T wave, but clinically inadequate limits of agreement with respect to ST-segment deviation, between the electrocardiographer and the computer. The optimal cut-off points were 0.115 mV (sensitivity 89%, specificity 98%) for the computer program to detect ST elevation ≥0.2 mV and 0.045 mV (sensitivity 74%, specificity 99%) for revealing ST elevation ≥0.1 mV. It was found that automatically measured ST-segment deviations were smaller than those manually measured. In conclusion, a correction should be performed to obtain optimal results in the automated analysis of ECGs, because the results have important implications for clinical decision making. **© 2005 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2005;96:1584–1588)**

Testing the accuracy of lead-specific measurements of the J point, the ST segment, and the T wave by computer programs in comparison with manual measurements by physicians is of crucial importance in developing computerized analysis algorithms. Very little is known about the correlation of these measurements. We could not find any previous study published in English comparing the correlation between manual and computerized measurements of the J point, the ST segment, and the T wave from 12-lead electrocardiograms (ECGs). The aims of our study were (1) to compare lead-specific computer-based measurements with those made by 2 experienced cardiologists and (2) to define values of computer-based measurements that would correspond to manually measured clinical cut-off values for significant ST-segment deviation.

Methods

The ECGs used in this study were collected in 69 consecutive patients hospitalized for suspected acute coronary syndrome in the Turku University Central Hospital from May 2000 to July 2001. The criteria for inclusion were the existence of a digitally recorded ECG at admission and an angiogram performed during the hospital stay. Exclusion criteria were left bundle branch block (n = 1) and pacemaker ECG (n = 3). The ECGs were recorded with a Marquette 12 SL machine (Marquette Electronics Inc., Milwaukee, Wisconsin), used routinely in the hospital.

Paper copies of the 69 ECGs recorded at admission were independently interpreted, retrospectively and in a random order, by 2 cardiologists without knowledge of the results of the computerized interpretations. Single measurement of the

[a]Heart Center and [b]Research Unit, Tampere University Hospital, Tampere; [c]Department of Medicine, University of Helsinki, Helsinki; [d]School of Public Health, University of Tampere, Tampere; and [e]Department of Medicine, University of Turku, Turku, Finland. Manuscript received April 13, 2005; revised manuscript received and accepted July 7, 2005.

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*Corresponding author: Tel: 358-3-311-66080; fax: 358-3-311-64157.
E-mail address: markku.eskola@pshp.fi. (M.J. Eskola).

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Table 1
The principles of κ value interpretation

Value of κ	Strength of Agreement
≤0.20	Poor
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Good
0.81–1.00	Very good

J-point, ST-segment, and T-wave changes were measured separately from all 12 leads with the aid of a handheld magnifying lens. On the basis of the study of Menown et al,[1] we measured ST-segment deviation at 80 ms after the J point, while the isoelectric line was determined by drawing a line between subsequent PQ segments.[1] Maximal T-wave deviation from the isoelectric line was measured ≥120 ms after the J point. All manual measurements were rounded off to the nearest 0.05 mV.

As part of the coding package, the Marquette 12 SL offers a data matrix.[2] This is a matrix with the 12 leads presented as rows and selected attributes of the P, Q, R, and S waves and displacements of the ST segment at the J point and at the midpoint of the ST segment and the amplitudes of T waves as columns. The data presented in the data matrix describe the median complex generated by the Marquette 12 SL system. The use of this data matrix in a personal computer has been previously described.[3]

We compared manually measured deviations at the J point, the ST segment, and the T wave with those measured by the computer and expressed in the data matrix, excluding lead aVR. We chose 3 numerical cut-off points for comparison on the basis of their clinical importance: (1) 0.2 mV for reperfusion therapy in anterior myocardial infarction, (2) 0.1 mV for inferior myocardial infarction, and (3) 0.05 mV for clinically significant ST depression.[4,5] After comparing all leads except lead aVR, we selected leads V_2, V_3, and LIII for additional statistical analysis because these leads are of most critical importance in anatomic interpretation of ECGs.[6]

The study was approved by the Ethics Committee of Turku University Central Hospital, and written consent was obtained from hospital-admitted study participants.

Statistical analysis: Agreement between categorical assessments (e.g., ST-segment elevation ≥0.2 mV) was described by κ statistics. Kappa describes the strength of agreement as a proportion of the possible scope for doing better than chance. Kappa has a maximum of 1.00 for perfect agreement, whereas 0 indicates no agreement better than could be expected by chance.[7] A generally accepted mode of κ value interpretation is listed in Table 1.

We tested the optimal cut-off points for the computer program to detect true ST-segment elevation using measurements made by cardiologists as a gold standard. We began the analysis by constructing scatterplots of the measured ST-segment deviations. Then, we performed cross-tabulations in an attempt to increase the sensitivity for the detection of actual ST elevation without decreasing specificity from 98%.

We used the Bland-Altman[8] statistical method for assessing agreement between the 2 methods of electrocardiographic measurements. First, we compared interobserver agreement between 2 cardiologists, and second, we compared agreement between computerized measurements and 1 cardiologist. The calculated mean difference between measured values ± 2 standard deviations of the differences was considered the limit of agreement. The difference between 2 measurements and their mean was plotted. Bland-Altman plots were created to show the differences in measurements between the 2 cardiologists and 1 cardiologist versus the computer with the means of the measurements.

All calculations were performed with the SPSS 12.0 statistical package (SPSS, Inc., Chicago, Illinois).

Results

The interobserver agreements between the 2 cardiologists were very good regarding the determination of ST-segment elevation ≥0.2 and 0.1 mV (κ = 0.91 and 0.85, respectively).

The cardiologists and the computer measured ST-segment deviations in a total of 759 leads, excluding lead aVR. For the entire electrocardiographic database, the agreement between 1 cardiologist and the computer in the determination of ST-segment elevation ≥0.2 mV was good (κ = 0.63). The correlation was moderate between the cardiologist and the computer in the determination of ST-segment deviation ≥0.1 mV (κ = 0.51).

Compared with manual analysis, the computer underestimated the ST-segment deflection (Figure 1). When the ST-segment elevation was 0.1 mV measured manually at 80 ms after the J point (n = 163 leads), the corresponding mean of the computer measurements of the ST-deviation was 0.053 ± 0.035 mV. Computer-based mean ST-segment deviation was 0.152 ± 0.048 mV in 61 leads with manually measured ST elevations of 0.2 mV.

Cut-off points: We tested different cut-off points to demonstrate the optimal computerized value in millivolts to detect true ST-segment elevation ≥0.2 and 0.1 mV, respectively. Table 2 shows the resulting sensitivity and specificity values. The clinically optimal cut-off point for computer-based deviation to separate true ST-segment elevation ≥0.2 mV was 0.115 mV, with a sensitivity of 89% and a specificity of 98%. The optimal cut-off point to find ST elevation ≥0.1 mV was 0.045 mV, with a sensitivity of 76% and a specificity of 98%.

Agreement in clinically important leads V_2, V_3 and LIII: The interobserver reliability in the determination of ST-segment deviation ≥0.2 mV in leads V_2 and V_3 and ≥0.1 mV in lead LIII was very good (κ = 0.94, 0.93, and

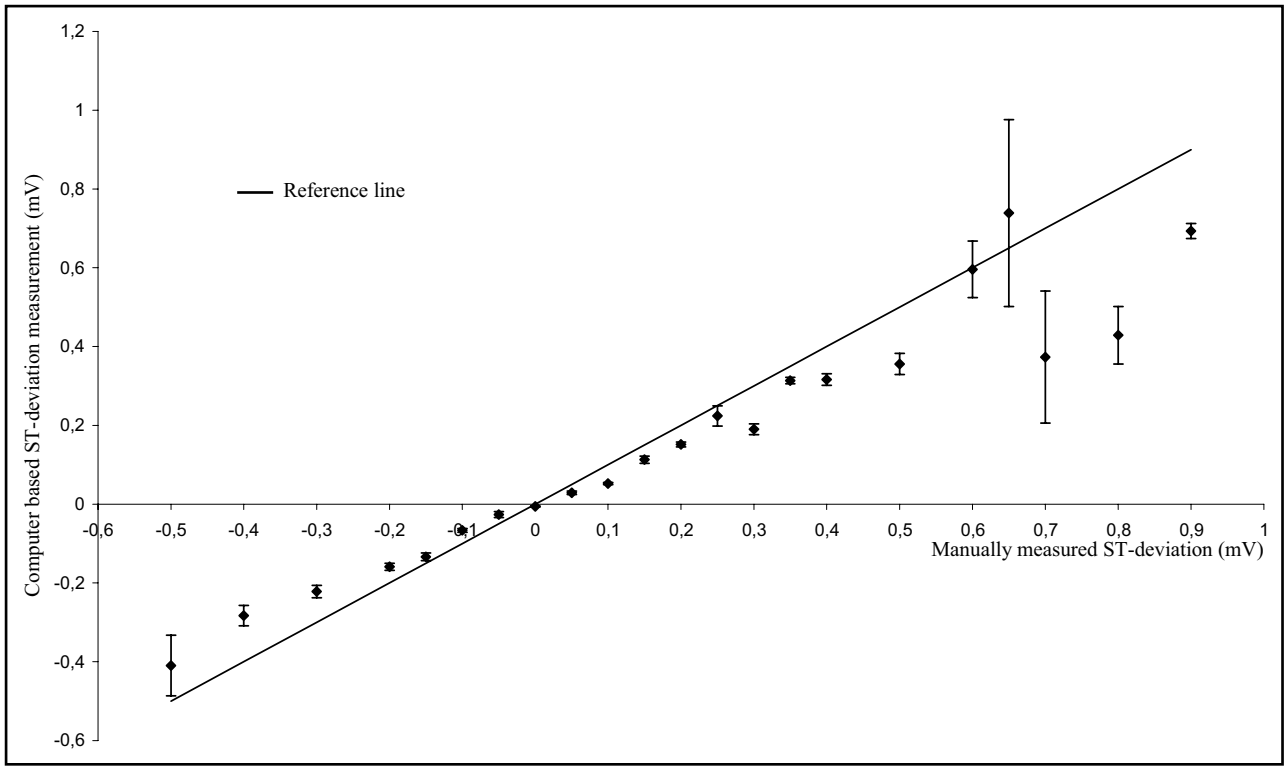

Figure 1. Variability of measured ST-segment deflections between 1 cardiologist and computer-based measurements (n = 759). Manually measured and computer-based ST-deviation measurements are given in millivolts. The *diamond* and the *error bars* represent the mean and the standard error of the mean computer measurement corresponding to the specific measurement made by 1 cardiologist. The manual measurements were made to the nearest 0.05 mV. Especially when comparing ST-segment depression measurements, the computer-based measurements tended to be smaller than the manually measured ST-segment deviations.

Table 2
Sensitivity and specificity of different cut-off points for the computer program to detect true ST-segment elevation

	Sensitivity (%)	Specificity (%)
True ST elevation ≥0.2 mV		
0.115 mV	89	98
0.120 mV	87	98
0.125 mV	85	98
True ST elevation ≥0.1 mV		
0.04 mV	80	97
0.045 mV	76	98
0.05 mV	74	99

Table 3
The agreement between one cardiologist and the computer regarding the ST-segment deflection in leads V_3, V_2, and LIII

	Lead	Value of κ
ST elevation (mV)		
≥0.2	V_3	0.85
≥0.2	V_2	0.75
≥0.1	LIII	0.52
ST depression (mV)		
≥0.05	LIII	0.79

0.80, respectively). The agreement between the 2 cardiologists was also very good regarding the determination of ST-segment depression ≥0.05 mV in lead LIII (κ = 0.86).

One cardiologist and the computer interpreted ST-segment elevation ≥0.2 mV in lead V_3 with very good agreement (κ = 0.85) and in lead V_2 with good agreement (κ = 0.72). In lead LIII, the agreement was better for measurements of ST depression than ST elevation (Table 3).

Bland-Altman analysis for assessing agreement: Bland-Altman analysis of measured deviations of the J point and the T wave from 1 cardiologist and the computer demonstrated acceptable limits of agreement. However, the test showed clinically unacceptable limits of agreement comparing measurements of the ST-segment deviations between 1 cardiologist and the computer. The limits of agreement were excellent between the 2 cardiologists when comparing J-point, ST-segment, and T-wave amplitude measurements (Figure 2).

Discussion

In this study, we compared lead-specific computer-based measurements with those made by an experienced cardiologist. In the study, there was a trend that automatically measured ST-segment deviations were smaller than those manually measured. It has been shown that computer-mea-

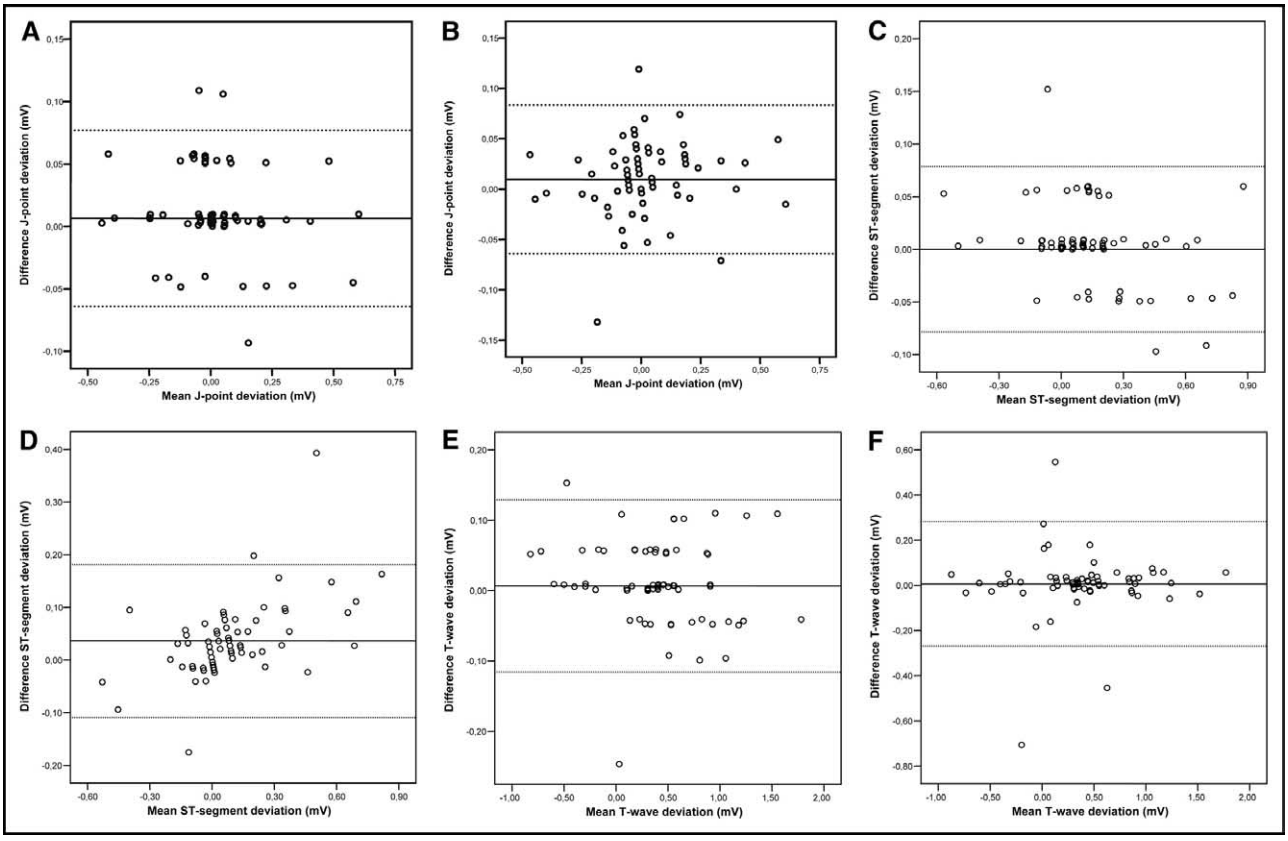

Figure 2. Bland-Altman diagrams of J-point, ST-segment, and T-wave deviations, demonstrating the mean difference *(solid line)* and limits of agreement *(dotted line)* (n = 69) between 2 cardiologists compared with measurements of J-point deviation in lead V_3 *(A)*, 1 cardiologist and computer-based measurements of J-point deviation in lead V_3 *(B)*, 2 cardiologists' measurements of ST-segment deviation in lead V_2 *(C)*, 1 cardiologist and computer-based measurements of ST-segment deviation in lead V_3 *(D)*, 2 cardiologists' measurements of T-wave deviation in lead V_3 *(E)*, and 1 cardiologist and computer-based measurements of T-wave deviation in lead V_3 *(F)*.

sured Q-wave durations are longer than those measured manually,[9,10] resulting in larger injury score results.[11] In Holter monitoring, automated analysis overestimates the incidence of myocardial ischemia.[12] In a previous study by Pelter et al,[13] another computer-based program overestimated ST deviation during ischemic episodes. In our study, a manually measured 1.2-mV ST elevation corresponded to a mean measurement of 0.152 mV by the computer (Figure 1). The difference between these 2 methods is mainly caused by different measurement points. There is no common agreement on what time point to use to measure ST amplitude. In this study, it was measured at 80 ms after the J point by manual measurement, while the computer selected a displacement at the midpoint of the ST segment.[2] The Marquette 12 SL data matrix does not allow measurement at J point + 80 ms. According to our results, comparisons between computer-based and cardiologist measurements of J-point and T-wave deflections were considered to be within the limits of agreement in Bland-Altman analysis.

When looking for optimal cut-off values for significant ST-segment deviations, our aim was to avoid a clinical scenario whereby reperfusion therapy would cause complications in patients without coronary occlusions. Hence, we decided to keep the specificity close to 100% to avoid false-positive cases. Automated electrocardiographic analysis has already been used in decision making in thrombolytic therapy.[14] Still, using strict electrocardiographic criteria would lead to the overuse and commercial automated analysis to the underuse of thrombolytic therapy.[15] We found that the optimal cut-off point was 0.115 mV for the computer program to detect true ST-segment elevations ≥0.2 mV when using the interpretation of an expert electrocardiographer as a gold standard. The corresponding value was 0.045 mV for an actual ST elevation ≥0.1 mV. Those cut-off points were used to maintain the specificity at ≥98% in connection with an acceptable sensitivity. Elko and Rowlandson[2] reported that the computerized interpretation of anterior acute myocardial infarction had a sensitivity of 79% and a specificity of 93% when the Marquette 12 SL program measured ST deviation at the end of the ST segment and a sensitivity of a 75% and a specificity of 91% when it measured at the midpoint of the ST segment. We assume that these midpoint results would be better if correction for the difference were performed. These findings emphasize the importance of using an expert electrocardiographer's interpretations as a gold standard when analyzing computerized measurements or introducing new computer-based diagnostic tools in clinical situations. The principal

finding of our study is that the accuracy of the computerized measurement of ST elevation is insufficient and that precise cut-off points should be used in commercial automated analysis algorithms for optimal clinical decision making.

The results of our study indicate that interobserver variation between 2 cardiologists is minimal when comparing J-point, ST-segment, and T-wave deviations measured from digitally recorded 12-lead ECGs. Kappa coefficients revealed that interobserver comparative accuracy was very good in all the measurements. The study of Goodacre et al[16] showed very good agreement regarding the interpretation of digitally acquired ECGs among experienced electrocardiographers, but junior doctors had a high error rate in reporting ECGs. A report from a large, randomized trial demonstrated that there are considerable differences between the on-site interpretation of admission ECGs and blinded evaluations performed in a core laboratory regarding relatively simple electrocardiographic variables.[17]

When developing different computer models, one should observe the ST-segment measurement disagreement between expert electrocardiographers and automated analysis.

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Detection of Proximal Coronary Occlusion in Acute Coronary Syndrome: A Feasibility Study Using Computerized Electrocardiographic Analysis

Markku J. Eskola, M.D.,* Kjell C. Nikus, M.D.,* Liisa-Maria Voipio-Pulkki, M.D., Ph.D.,† Heini Huhtala, M.Sc.,‡ Juha Lund, M.D.,§ Tuomo Ilva, M.D.,§ Kari O. Niemelä, M.D., Ph.D.,* and Pekka Porela, M.D., Ph.D.§

*From the *Heart Center, Tampere University Hospital, Tampere, Finland; †Department of Medicine, University of Helsinki, Helsinki, Finland; ‡School of Public Health, University of Tampere, Tampere, Finland; and §Department of Medicine, University of Turku, Turku, Finland*

Background: Rapid identification of a proximal occlusion site of a major coronary artery is of paramount importance in the care of myocardial infarction (MI). It is increasingly recognized that routine electrocardiogram (ECG) can be used for that purpose, provided that expert interpretation is available. Computer-based signal analysis has potential to enhance early ECG interpretation but its performance must be validated against manual algorithms. We therefore set out to develop a computer-assisted model to detect proximal occlusion of the left anterior descending coronary artery (LAD) in patients with suspected acute coronary syndrome (ACS).

Methods: Based on manual anatomical interpretation of the ECG, obtained from 216 consecutive patients who were admitted due to suspected ACS, an automatic computerized ECG model to detect LAD occlusion was constructed. Agreement between manual evaluation of the ECG by two cardiologists and a computerized ECG algorithm to detect occlusion of the LAD and the site of occlusion was determined.

Results: Using an expert electrocardiographer's anatomical interpretation as the gold standard, the computer model recognized patients fulfilling ECG criteria for any occlusion of the LAD with a specificity of 99% and a sensitivity of 67% ($\kappa = 0.71$). However, proximal LAD occlusion was detected with 100% specificity and 86% sensitivity ($\kappa = 0.72$). The computer program detected a distal occlusion in the LAD with a specificity of 99% and a sensitivity of 40% ($\kappa = 0.72$).

Conclusions: Computerized anatomical interpretation of the ECG is feasible and allows detection of a proximal LAD occlusion with excellent accuracy. **A.N.E. 2007;12(4):301–305**

electrocardiogram; computerized interpretation; acute coronary syndrome; myocardial infarction

The electrocardiogram (ECG) is still the most readily available and fastest method for the diagnosis of acute myocardial infarction (MI). In acute anterior ST-elevation MI, the left anterior descending (LAD) coronary artery is almost exclusively the infarct related artery (IRA). Proximal LAD occlusion (prior to the first diagonal branch) has a remarkably poor prognosis due to extensive area at risk.[1] As patients with proximal occlusions may benefit most from early reperfusion therapy several manual ECG algorithms have been proposed to differentiate proximal versus distal LAD artery occlusion in acute anterior MI.[2] Because ECG interpretation is often made by paramedics in

Address for reprints: Markku J. Eskola, M.D., Heart Center, Tampere University Hospital, Biokatu 6, P.O. Box 2000, 33520 Tampere, Finland. Fax: +358–3-311-64157; E-mail: markku.eskola@pshp.fi

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out-of-hospital settings, computer-based anatomical interpretation programs could help to identify such patients without delay. Moreover, clinical trials of thrombolytic therapy have shown that reduction in mortality is greatest when the reperfusion of the IRA is achieved very early after the onset of ischemia.[3]

We are not aware of any previous publications concerning computer-based anatomical ECG interpretation in MI. This approach should add to the early characterization and treatment of an anterior MI. We therefore set out to develop and validate a computer model for anatomical interpretation of anterior MI using manual ECG analysis as the golden standard in patients with anterior ST-elevation MI.

METHODS

Subjects

The original study population consisted of 531 consecutive patients hospitalized for suspected acute coronary syndrome in the Turku University Hospital between May 2000 and July 2001 and who participated in a myocardial injury marker study.[4] The study protocol had been approved by the Ethics Committee of Turku University Hospital and written informed consent was obtained from all patients.

For the purposes of this study, patients with a digitally recorded ECG at admission (n = 369) were selected. Exclusion criteria were left bundle branch block (n = 25), left ventricular hypertrophy (n = 26), pathological Q wave (n = 47), wide QRS duration (n = 42), pacemaker ECG (n = 9), and poor technical ECG quality (n = 4). All exclusions were made by manual interpretation. A total of 216/369 (59 %) patients were included in the final study group. The ECG's were recorded by a Marquette 12SL machine (Marquette Electronics Inc., Milwaukee, WI) routinely used in the hospital.

ECG Analysis

Paper copies of the 216 ECG's recorded at admission were independently interpreted off-line and in a random order by two cardiologists without knowledge of the patients' clinical details or the results of the computerized interpretation. Single values of the J-point and the ST-segment changes were measured separately from all 12 leads with the aid of a hand held magnifying lens. ST-segment deviation from the isoelectric line, determined by drawing a line between subsequent PQ segments, was measured at 80 ms after the J point. All manual measurements were rounded off to the nearest 0.05 mV.

Pathological Q waves were defined as follows: (1) in leads V_{1-3} any Q wave $\geq$30 ms in duration, (2) in leads I, II, aVL, aVF, V_{4-6} a Q wave $\geq$0.1 mV in height and $\geq$30 msec in duration in $\geq$2 adjacent leads and 3) in leads V_{1-2} R-wave duration >40 ms and R/S ratio >1 in the absence of pre-excitation, right ventricular hypertrophy or right bundle branch block. ST-elevation MI was diagnosed in the presence of clinically appropriate symptoms in patients with ST-segment elevation $\geq$0.2 mV in V_1 through V_3 and $\geq$0.1 mV in other leads and an increased value of cardiac troponin I.[5]

Manual anatomical interpretation of the ECG was made in the cases with anterior ST-elevation MI's. The anatomical classification of the LAD artery occlusion was made by the following criterions: (1) the LAD artery was interpreted as the IRA if maximal ST-segment elevation ($\geq$0.2 mV) was present in leads V_2–V_3;[6] (2) the site of occlusion in respect to the side branches was determined according to previously published revised criteria.[7–8] Birnbaum et al. found that ST depression in the inferior leads predicts a culprit lesion proximal to the origin of the first diagonal branch.[7] According to Arbane et al., mean ST segments were elevated in aVL when the culprit lesion was the proximal LAD.[8] In this study, a proximal lesion in the LAD artery was defined as ST-segment elevation $\geq$0.05 mV in lead aVL and ST-depression $\geq$0.05 mV in LIII (Fig. 1). All other ECG morphologies were classified as distal occlusion.

As part of the coding package, the Marquette 12SL offers a data matrix including, for example Q-wave amplitude and duration, displacement of the ST-segment (*J*-point, mid and end of ST) and of the T-wave for all leads.[9] The ST-segment displacements were collected from the data matrix and used for off-line analysis in a personal computer (PC) as previously described.[10] An automatic PC interpretation program for the detection and anatomical classification of LAD occlusion was constructed using the above mentioned criteria and applied to the data of the 261 patients with suspected ACS. In addition to uncorrected cutoff points (as expressed in the data matrix), we used corrected cutoffs for the computer program to detect equivalents of manual

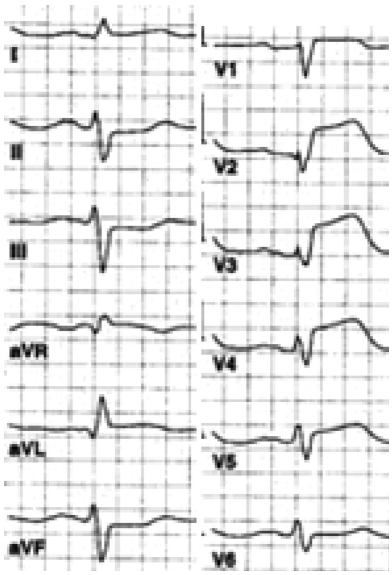

Figure 1. Maximal ST-segment elevation in leads V_2-V_3 indicates that the left anterior descending coronary artery is the infarct related artery. The presence of ST-segment elevation ≥0.05 mV in lead aVL and ST-segment depression in lead LIII as a reciprocal change is a sign of an occlusion proximal to the first diagonal side branch.

ST-elevations of ≥ 0.2 mV and ≥0.1 mV and ST-depressions of ≥0.05 mV as reported previously.[11]

For the purposes of this study, we also determined that the optimal computerized cutoff value to detect the equivalent of manual ST-segment elevation ≥0.05 mV. In brief, we began the analysis by constructing scatter plots of all measured ST-segment deviations. We then performed cross-tabulations in an attempt to increase the sensitivity for detection of actual ST-elevation without decreasing specificity from 98%.[11] The optimal computerized cutoff was found to be 0.035 mV with a sensitivity of 79 % and a specificity of 98%.

Statistical Analysis

Agreement between categorical assessments was described by Kappa (κ) statistics. Kappa describes the strength of agreement as a proportion of the possible scope for doing better than chance. Kappa has a maximum of 1.00 for perfect agreement, 0 indicates no agreement better than could be expected by chance.[12]

We tested the uncorrected and corrected cut-off points for the computer program to detect the occlusion in the LAD artery using interpretations and measurements made by cardiologists as a gold standard. Sensitivity and specificity values were calculated.

All calculations were performed with the SPSS 12.0 statistical package. (SPSS, Chicago, IL)

RESULTS

The manual anatomical interpretation of the ECG indicated that the LAD was the IRA in 12 of the 216 patients (6%) with suspected acute coronary syndrome (ACS). The site of the occlusion was proximal in 7 (58%) of these patients (SPSS, Chicago, IL).

The sensitivities, specificities and the κ values of the computer program to detect various LAD occlusions are shown in Table 1. Both the uncorrected and corrected computer programs were able to determine the occlusion in the LAD with a high specificity (99%) when using manual interpretation as a gold standard. However, the use of ST-segment corrections improved the sensitivity to detect the occlusion in the LAD (a sensitivity of 58% with uncorrected and 67% with corrected computer program). The agreement between the manual analysis and the uncorrected or corrected computer program in the determination of the LAD as an IRA was good ($\kappa = 0.65$ and $\kappa = 0.71$, respectively).

Table 1. Sensitivity, Specificity and κ values of Uncorrected and Corrected Computer Program to Detect Site of Occlusion of the Left Anterior Descending (LAD) Coronary Artery in Patients with Acute Coronary Syndrome When Using Manual Interpretation as a Gold Standard, n = 216

	Uncorrected Computer Program			Corrected Computer Program		
Site of Occlusion	**Sensitivity**	**Specificity**	**Value of κ**	**Sensitivity**	**Specificity**	**Value of κ**
LAD	58	99	0.65	67	99	0.71
LAD proximal	86	100	0.65	86	100	0.72
LAD distal	20	99	0.65	40	99	0.72

The use of ST-segment corrections also improved the ability to determine the level of the LAD occlusion. The sensitivity and specificity of the uncorrected and corrected computer program to detect proximal occlusion in the LAD were similar (86% vs 100%, respectively). However, the correlation between the manual and the uncorrected versus corrected computer program to define the site of a proximal occlusion in the LAD artery was better with the corrected than uncorrected ST-segment cutoff points ($\kappa = 0.72$ vs $\kappa = 0.65$, respectively). The corrected computer program was more sensitive to detect distal occlusions in the LAD artery than the uncorrected program (sensitivity 40% vs 20%, respectively), while there was no difference in specificity (99% in both analysis).

An expert electrocardiographer and the corrected computer program interpreted the ECG finding of distal occlusion in the LAD with good agreement ($\kappa = 0.72$).

DISCUSSION

This study represents the first attempt to compare computer based with manual ECG interpretation to perform an anatomical ECG interpretation. We hypothesized that it would be possible to construct a computer program for recognizing patients with occlusion of the LAD artery with a good correlation with manual interpretation of ECG. The study population consisted of the whole spectrum of ACS patients. We used cutoff points for significant ST-segment deviations (≥ 0.2, ≥ 0.1, $\geq +0.05$ and ≥ -0.05 mV). Those ST-deviations are the most critical in the algorithm for anatomical interpretation. We compared computerized interpretations between uncorrected (expressed in the data matrix) and corrected measurements (cutoff points). The specificity of uncorrected and corrected computer programs to detect the LAD as an IRA and the site of LAD occlusion based on ECG criteria was good compared to manual measurements. The use of ST-segment correction improved the sensitivity to predict the LAD as the IRA and to localize the culprit lesion to the distal part of the LAD artery. Hence, the use of corrected ST-segment cutoff values improved the results of automated ECG interpretation. Taken together, the computer program was able to detect an LAD-related ST-elevation MI with a sensitivity of 67% and a specificity of 99% when using interpretation of two cardiologists as a gold standard. Computer-assisted interpretation to predict a proximal LAD artery occlusion resulted in high sensitivity and specificity (86% vs 100%, respectively). In reality, the capability of the computer assisted anatomic ECG interpretation to find proximal LAD lesions is poorer. In our study, the ECG criteria for proximal LAD lesion were not tested against coronary angiography. In such studies, ≥ 0.05 mV ST-elevation in lead aVL had 73% sensitivity and 78% specificity to predict a proximal LAD lesion.[13]

It is clinically important to recognize patients with an acute occlusion of the proximal LAD, which can result in an extensive anterior wall MI. Such assessment should be simple, quick, and noninvasive.[14] We think that computer-based anatomical interpretation of the ECG has potentials to become an efficient tool for clinical decision making. The computers alone cannot give the final diagnosis, but computer-assisted interpretation is very helpful especially for paramedics and inexperienced emergency physicians by whom digitally recorded ECG is actually increasingly utilized. Maximal advantage of this development is possible by using clinically relevant automated ECG analysis programs. However, computer models should be validated using manual ECG interpretation as a gold standard.

The best diagnostic approach is one that combines the interpretation by a person and a machine.[15] There are some prerequisites for anatomic ECG interpretation. Absence of major confounding factors like left ventricular hypertrophy, left bundle branch block, and pacemaker ECG is of crucial importance. We excluded 153 patients after manual interpretation. This emphasizes the role of the manual interpretation, because computerized anatomic analysis is not possible in all cases.

There are several limitations to this study. The number of patients fulfilling criteria for LAD-related coronary occlusion was small. Hence, this represents a preliminary feasibility study. We used ECG as the golden standard to predict the culprit artery. Including coronary angiography findings in the statistical analyses could have given additional information. Also, cases with ECG confounders, like left bundle branch block, were excluded by manual interpretation. The power of the computer program to identify these ECGs was not tested.

We conclude that a computer program can recognize an occlusion of the proximal LAD artery with a good sensitivity and specificity in patients with ACS. We believe that our findings open new

opportunities for computerized analysis of the ECG. However, larger studies should be undertaken especially without manual ECG prescreening to establish the value of this automated ECG program to identify proximal LAD lesions.

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Value of the 12-lead electrocardiogram to define the level of obstruction in acute anterior wall myocardial infarction: Correlation to coronary angiography and clinical outcome in the DANAMI-2 trial ☆

Markku J. Eskola [a,*], Kjell C. Nikus [a], Lene Holmvang [b], Samuel Sclarovsky [c], Hans-Henrik Tilsted [d], Heini Huhtala [e], Kari O. Niemelä [a], Peter Clemmensen [b]

[a] *Heart Center, Department of Cardiology, Pirkanmaa Hospital District, Tampere, Finland*
[b] *Department of Cardiology B, Heart Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*
[c] *Procardia Medical Center, Tel Aviv, Israel*
[d] *Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark*
[e] *School of Public Health, University of Tampere, Tampere, Finland*

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Abstract

Background: Acute anterior myocardial infarction (MI) caused by proximal occlusion of the left anterior descending coronary artery (LAD), is associated with unfavourable outcome and should be recognized by simple noninvasive methods like the 12-lead electrocardiogram (ECG).
Methods: In a prospective post-hoc DANAMI-2 substudy we compared two pre-specified ECG patterns to determine the level of LAD occlusion. The ECG findings were correlated to coronary angiography from the acute phase. The impact on clinical outcome of ECG and angiographic signs of proximal versus distal LAD occlusion was studied.
Results: In 146 patients without confounding factors on the ECG, either ST-elevation ≥0.5 mm in lead aVL or any ST-elevation in lead aVR in association with precordial ST-segment elevation in at least two contiguous leads (including V_2, V_3 or V_4) had a sensitivity of 94%, specificity of 49%, positive predictive value of 85% and negative predictive value of 71% to predict a proximal LAD lesion. Surprisingly, ECG or angiographic signs of lesion proximality were not associated with worse outcome at 30 day or 2.7 year follow-up.
Conclusions: The site of occlusion in the LAD could be reliably predicted by 12-lead ECG in patients with acute anterior MI. The prognostic significance of the level of occlusion in the LAD in the modern era of acute ST-elevation MI treatment should be reassessed.
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Keywords: Electrocardiogram; Myocardial infarction; Prognosis

1. Introduction

Immediate reperfusion, preferably by primary percutaneous coronary intervention (PCI), is the preferred treatment for acute ST-elevation myocardial infarction (STEMI). Not all health care systems can provide 24/7 invasive service. Therefore it is important to identify high-risk subgroups by noninvasive methods. In acute anterior STEMI, the site of occlusion in the left anterior descending coronary artery (LAD) is related to the extent of myocardial necrosis and prognosis [1–5]. The myocardial area at-risk is more

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* Corresponding author. Heart Center, Tampere University Hospital, Biokatu 6, P.O. Box 2000, 33520 Tampere, Finland. Tel.: +358 3 311 66080; fax: +358 3 311 64157.
E-mail address: markku.eskola@pshp.fi (M.J. Eskola).

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extensive if the occlusion is located proximal to a clinically significant side branch compared to a distally located lesion.

Sudden occlusion of a coronary artery or a major side branch, results within seconds in positive and tall T waves in the electrocardiogram (ECG) [6]. If the artery remains occluded the ECG will show signs of regional transmural ischaemia – elevation of the ST-segment ("injury vector") – within minutes. In patients with acute chest pain this *preinfarction syndrome* represents the window of opportunity to treat before irreversible myocardial damage develops [7]. The ECG from this stage contains valuable information about the coronary anatomy [8]. The majority of patients with the preinfarction syndrome will evolve toward myocardial infarction (MI) with or without Q waves (*evolving MI*).

Previous studies have demonstrated that the ECG is useful in defining the level of obstruction in the LAD in acute anterior STEMI. ST-elevation in the extremity leads I and aVL, reciprocal ST-depression in the inferior leads II, III and aVF and ST-elevation in lead aVR have been associated to a culprit lesion in the proximal part of the artery [9–12]. The ECG markers have shown varying sensitivity and specificity and most studies have been retrospective. No large prospective studies with coronary angiography from the acute phase have been published.

The main purpose of our study was to assess the role of two pre-specified ECG patterns to predict the occlusion site of the LAD in relation to the diagonal side branches in a large patient cohort with coronary angiography from the acute phase. In addition we performed two secondary analyses: 1) the value of the ECG to predict the LAD as the culprit artery, and 2) the impact on clinical outcome of ECG and angiographic signs of proximal versus distal LAD occlusion.

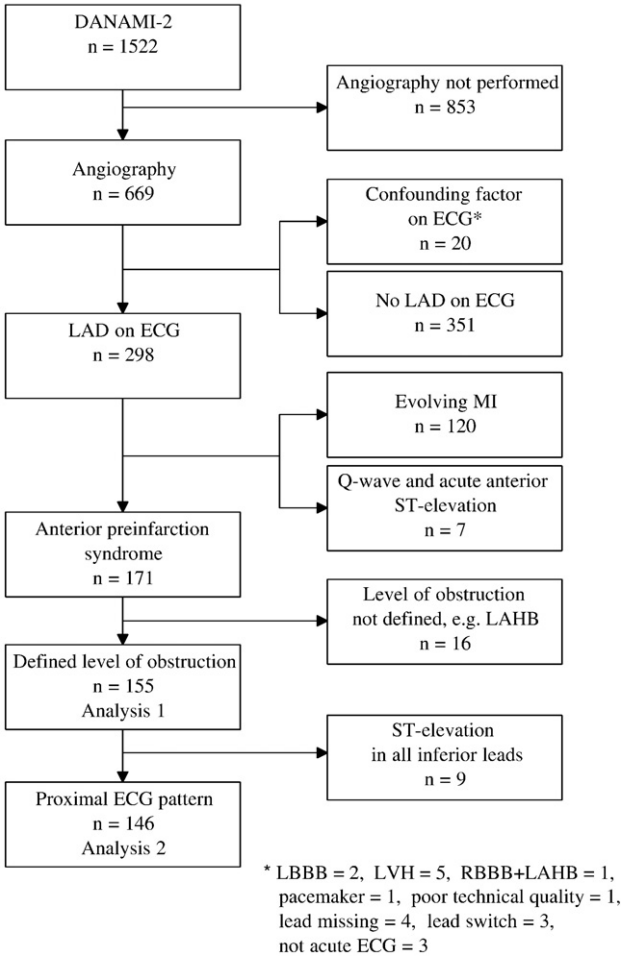

Fig. 1. This flow chart shows the subgroups of the patients defined by ECG and the principles of the analyses performed. LAD on ECG is defined as maximal ST-elevation ≥2 mm in at least two contiguous leads V_2–V_4.

2. Material and methods

2.1. Patient population

The DANAMI-2 trial randomized 1572 patients with ST-segment elevation acute MI to either primary angioplasty or fibrinolysis with intravenous alteplase. A detailed description of inclusion and exclusion criteria for the DANAMI-2 trial has been reported previously [13]. The primary end point was a composite of mortality, clinical infarction and disabling stroke at 30 days. The study was approved by the National Ethics Committee of Denmark. All eligible patients provided written informed consent.

The flow chart in Fig. 1 illustrates the subgroups of the patients and the principles of the analyses performed in the present substudy. Re-analysis of all the qualifying ECGs in the trial was required. We were unable to properly confirm the patient study number and/or timing of the ECG in 19 patients, and 31 randomization ECGs were never sent to the core laboratory. Of the remaining 1522 patients, 649 had coronary angiography in the acute phase and no confounding factor (listed in the flow chart) on the ECG. These patients were included in the secondary analysis to predict the LAD as the culprit artery based on pre-specified ECG criteria. For the main analysis – determining the angiographic level of occlusion in the LAD by ECG criteria – we included patients (n = 155) with ECG signs of the preinfarction syndrome, who did not present intraventricular conduction disturbances. Hence, those with evolving MI defined by established pathological Q waves and/or signs of reperfusion by negative or biphasic T waves were excluded [7]. Pathological Q waves were defined as follows: 1) in leads $V_{1–3}$ any Q wave ≥30 ms in duration, 2) in leads I, II, aVL, aVF, $V_{4–6}$ Q wave ≥1 mm in height and ≥30 ms in duration in ≥2 adjacent leads and 3) in leads $V_{1–2}$ R-wave duration >40 ms and R/S ratio >1 in the absence of pre-excitation, right ventricular hypertrophy or right bundle branch block.

2.2. ECG analysis

Randomization ECGs were analyzed by three investigators blinded to the clinical data and angiographic findings at the independent core laboratory at Tampere University Hospital. Any disagreement between the investigators was

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Table 1
Baseline characteristics of patients with LAD occlusion on the ECG ($n=298$) according to different ECG patterns

	Anterior preinfarction syndrome $N=171$ %	Other acute anterior MI[a] $N=127$ %	p-value
Age (year)[b]	62 (53–74)	65 (53–74)	0.46
Gender (males)	74	72	0.46
Hypertension	13	17	0.23
Diabetes (NIDDM + IDDM)	8	6	0.68
Current smoking	62	54	0.30
Previous MI	12	10	0.41
Previous PCI	2	4	0.32
Previous stroke	4	4	0.60
Heart rate (beats/min)[b]	74 (61–85)	70 (59–85)	0.33
Systolic blood pressure (mmHg)[b]	136 (120–150)	138 (115–150)	0.97
Medical treatment			
Aspirin	21	23	0.36
Beta-blockers	14	12	0.41
ACE-inhibitors	5	8	0.25
Calcium antagonists	9	10	0.56
Nitrate	9	6	0.29
Diuretics	13	13	0.51
Lipid-lowering drugs	5	7	0.33
Coumarins	2	3	0.47
Time to randomization ECG[b]	01:35 (00:58–02:35)	02:38 (01:34–06:11)	<0.001
Time to PCI (balloon)[b]	03:12 (02:35–04:20)	04:24 (03:17–08:08)	<0.001
Estimated EF after PCI (echo)[b]	50 (40–60)	50 (45–60)	0.75

NIDDM = non-insulin dependent diabetes mellitus; IDDM = insulin dependent diabetes mellitus; MI = myocardial infarction; PCI = percutaneous coronary intervention; ACE = angiotensin-converting enzyme; EF = ejection fraction; Echo = echocardiography.

[a]Anterior evolving MI ($N=120$) or Q waves in leads other than V_2–V_4 in association with acute anterior ST-elevation MI ($N=7$).

[b]Variables are given as percentages or median values followed by interquartile ranges, time in hours and minutes.

resolved by consensus. The ST-segment was measured manually at the J point with the TP-segment as the isoelectric line. The LAD was defined as the culprit artery in patients with maximal ST-elevation ≥2 mm in at least two contiguous leads V_2–V_4.

We compared two pre-specified ECG patterns to determine the level of LAD occlusion based on the 12-lead ECG. Occlusion in the proximal part of the LAD was defined by 1) concomitant ST-elevation ≥0.5 mm in lead aVL (aVL+ pattern) or 2) either ST-elevation ≥0.5 mm in lead aVL or any ST-elevation in lead aVR (aVR+ pattern) (analysis 1 in Fig. 1). An additional analysis (proximal pattern) (analysis 2 in Fig. 1) was performed after excluding patients ($n=9$) with concomitant ST-elevation ≥1 mm in all inferior leads. All other ECG morphologies were classified as distal occlusion. The ECG findings were correlated to coronary angiography.

2.3. Coronary angiography

One investigator at the core laboratory at Aalborg University Hospital analyzed all angiograms blinded to the clinical and ECG data. The culprit artery was defined. When more than one lesion was present in the LAD, the site of the culprit lesion was determined by the appearance of complete obstruction of the artery or by the more detailed angiographic characteristics of the lesion including presence of either residual thrombus or ulcerated plaque. The culprit lesion was considered proximal when located before a medium-to large-sized (≥1.5 mm) diagonal branch.

2.4. Clinical outcome

The impact of the level of occlusion on clinical outcome was studied in a secondary analysis. We used the same primary end point as in the main DANAMI-2 study — a composite of mortality, clinical infarction and disabling stroke at 30 days, and in addition, at 2.7 years. In the angiographic analysis, we used the previously mentioned definitions of proximal and distal occlusion. In the ECG analysis, we included patients ($n=307$) with signs of an LAD occlusion without ECG confounders treated with primary PCI ($n=146$) or fibrinolysis ($n=161$). We used the criteria for the proximal pattern for determining the occlusion site as mentioned above.

2.5. Statistical analysis

Categorical variables were expressed as numbers of patients or percentages and continuous variables as medians followed by interquartile range. For comparison of categorical variables the chi-square test or Fisher's exact test was used. The Mann–Whitney test was used for numerical variables. A probability value <0.05 was considered statistically significant. End point data between groups was compared by log rank test. Sensitivity, specificity, positive and negative

Table 2
The infarct related artery interpreted by angiogram in patients with LAD occlusion on the ECG ($n=298$) according to different ECG patterns

	Anterior preinfarction syndrome $N=171$	Other acute anterior MI[a] $N=127$	p-value
Infarct related artery			0.74
Left anterior descending	165	118	
Left circumflex	1	2	
Right coronary	2	3	
Diagonal branch	2	2	
Left obtuse marginal	1	2	

MI = myocardial infarction.

[a]Anterior evolving MI ($N=120$) or Q waves in leads other than V_2–V_4 in association with acute anterior ST-elevation MI ($N=7$).

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Table 3
The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the different ECG patterns to predict proximal occlusion of the left anterior descending coronary artery in patients with acute anterior myocardial infarction (concomitant ≥2 mm ST-elevation maximally in leads V_2–V_4)

ECG pattern	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
aVL+	82	50	84	45
aVR+	87	50	85	55
Proximal	94	49	85	71

aVL+ pattern = ST-elevation ≥0.5 mm in lead aVL; aVR+ pattern = either aVL+ pattern or any ST-elevation in lead aVR; Proximal pattern = aVR+ pattern excluding patients with ST-elevation ≥1 mm in all inferior leads.

predictive values were calculated. All calculations were performed with the SPSS 12.5 statistical package.

3. Results

Table 1 shows the baseline data of patients with LAD occlusion on the ECG (n=298). The median time from the onset of symptoms to recording of the randomization ECG and time to PCI was shorter in patients with anterior preinfarction syndrome compared to those with other acute anterior MI. Otherwise, the baseline characteristics of the patients were similar. The distribution of angiographic findings in the preinfarction syndrome (n=171) and in the other acute anterior MI groups (n=127) is presented in Table 2.

The pre-specified ECG criteria for LAD occlusion had a sensitivity of 87% and specificity of 96% to predict the angiographic culprit artery. Also the positive and negative predictive values were high, 95% and 88%, respectively.

In our main analysis, the sensitivity, specificity and predictive values of the different ECG patterns to predict the level of occlusion in respect to diagonal side branches are listed in Table 3. Proximal occlusion of the LAD could be predicted with a sensitivity of 94% and specificity of 49% by the prespecified proximal pattern. The corresponding positive and negative predictive values were 85% and 71%, respectively.

In patients treated with primary PCI, proximal LAD occlusion by ECG criteria (proximal pattern) was not associated with worse clinical outcome than distal occlusion at 30 days and at 2.7 years (composite endpoint 9% vs. 13%, p=0.57 and 21% vs. 17%, p=0.65, respectively). Neither was any statistically significant difference in mortality, clinical reinfarction and disabling stroke at 30 days and at 2.7 years observed between angiographically defined proximal versus distal occlusion (12% vs. 17%, p=0.39 and 23% vs. 26%, p=0.62, respectively).

In the entire study group (PCI and fibrinolysis arms), the rate of the primary composite end point was equal between proximal and distal occlusion defined by ECG (at 30 days and 2.7 years 21% vs. 18%, p=0.7 and 21% vs. 24%, p=0.63, respectively).

4. Discussion

This is to our knowledge the first large-scale prospective study to compare 12-lead ECG with coronary angiography findings from the acute phase and with clinical outcome. The results represent the diagnostic information from one single 12-lead ECG without data on past cardiovascular history like cardiomyopathies, prior MI, previous ECG findings or of the clinical condition of the patients. Our study shows, that in patients with acute anterior STEMI without pathological Q waves, inverted T waves or ECG confounders, like bundle branch block, the level of LAD occlusion in respect to significant side branches could be predicted with high sensitivity and moderate specificity. In addition, a culprit lesion in the LAD could be reliably predicted with a sensitivity of 87% and a specificity of 96% in a large cohort of STEMI patients even when patients with known ECG confounders like pathological Q waves and those with multivessel disease were included.

Many rather small retrospective studies comparing different ECG patterns with coronary anatomy to predict the culprit artery and the level of occlusion have been published. Most studies have excluded patients with multivessel disease, although this is often encountered in daily clinical practice [14]. Birnbaum et al. found that the presence of 1 mm of ST-elevation in leads I and aVL had a good positive predictive value for a pre-diagonal lesion [9]. However, the sensitivity of their criteria was poor (27, 46 and 27% for leads I, aVL and I+ aVL, respectively). ST-elevation in lead aVL (and usually also in lead I) in proximal LAD occlusion has been related to the first diagonal side branch, supplying the anterolateral wall, being occluded by the thrombotic process. The injury vector in anterolateral MIs is directed to the left shoulder towards leads I and aVL. Kim et al. reported high, 91%, sensitivity and 90% specificity of an ST-injury pattern in aVL in predicting a culprit lesion prior to the first diagonal branch [15]. Their study, however, also included patients in later stages of the infarct process than in the present study. Another limitation of the study was the timing of coronary angiography on average 6.3 days after the initial ECG. It may be difficult to assess whether the thrombotic process extended more proximally (e.g. covering a side branch) in the acute phase when the angiography is performed later in the disease process. Optimally both the ECG recording and the coronary angiography should be performed within close temporal proximity and during the acute phase of the MI process as in the present study. Koju et al. showed in a rather small patient cohort excluding patients with organic heart disease and previous MI that ≥0.5 mm ST-elevation in lead aVL and aVR had 73% and 42% sensitivity and 78% and 97% specificity, respectively, to predict a proximal LAD lesion [16]. In their study angiography was performed within two weeks from the acute phase.

We found that adding any ST-elevation in lead aVR to the definition of a proximal occlusion of the LAD irrespective of the changes in other extremity leads improved the sensitivity of the ECG analysis compared to using only ST-elevation in lead aVL (82 vs. 87%, respectively). Engelen et al showed that ST-elevation in lead aVR was a specific sign of a proximal LAD occlusion before the first septal branch [11]. However, the sensitivity of the ECG finding was low. They speculated that transmural ischaemia of the basal septum

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with an injury current directed to the right shoulder would explain the ECG finding. Alternatively, the ECG finding could express the pathophysiologic consequences of extensive ischaemia in the whole anterior wall, the majority of the ventricular septum and significant parts of the anterolateral wall, induced by a very proximal LAD occlusion. In patients with non-ST-elevation MI ST-segment elevation in lead aVR in addition to widespread ST-depression indicates 3-vessel or left main coronary artery disease [17,18]. In these cases extensive subendocardial ischaemia induced by severely elevated left ventricular end-diastolic pressure and diastolic dysfunction has been proposed.

Kosuge et al reported that the proximity of the culprit lesion in the LAD was similar in patients with ST-elevation, without ST-segment deviation or with ST-depression in aVR [19]. However, they only included patients with ST-elevation ≥ 2 mm in >2 contiguous precordial leads and ST-elevation ≥ 1 mm in leads I, aVL or both possibly resulting in a selection bias favoring the ECG pattern of proximal LAD occlusion.

We found the strongest correlation to coronary angiography findings when proximal occlusion electrocardiographically was defined as ≥ 0.5 mm ST-elevation either in lead aVL or any ST-elevation in aVR and when patients with 1 mm or more ST-elevation in all inferior leads were excluded from the analysis (sensitivity 94% and specificity 49%). A minority of patients with LAD occlusion show simultaneous ST-elevation in the precordial and the inferior leads II, III and aVF [20]. Autopsy reports have shown that in the majority of patients the LAD wraps around the LV apex and extends up the posterior interventricular sulcus to a variable extent [21]. Studies have shown that the proportion of patients with a large LAD wrapping around the apex is significantly higher in anterior MI patients with simultaneous inferior ST-elevation, and conversely significantly lower in those with ST-depression [22,23]. Occlusion in a big wrap-around the apex artery may result in ischaemia of two electrically opposite areas, the anterior and the inferior. This in turn may attenuate the ST elevations in the electrically opposite leads aVL and III resulting in an isoelectric or even depressed ST-segment in lead aVL despite a proximal LAD occlusion. Our finding that ST-elevation in lead aVL is a more sensitive marker of proximal LAD occlusion if patients with inferior ST-elevation were excluded from the analysis supports the findings of Birnbaum et al. that ST-elevation in lead aVL is not a reliable sign of a proximal lesion in the LAD in cases with ST-elevation in all inferior leads [9]. Hence, the size of the artery should be added as a variable when defining level of occlusion of the LAD.

Surprisingly, in the present study, contrary to prior publications, proximal LAD-related MI was not associated with worse clinical prognosis at 30 day or 2.7 year follow-up than distal occlusions either in patients treated with PCI or fibrinolysis. This was true both for ECG- and angiographically defined proximal LAD disease. Karha et al. found that proximal lesion in LAD was associated with a higher incidence of in-hospital death or recurrent acute MI compared with mid or distal lesions in patients with acute MI [3]. They used pooled data from four different trials comparing different pharmacological reperfusion therapies, and angiographic data were obtained 90 min after fibrinolytic administration. One possible explanation for the different results compared to our study could be the difficulty to identify the exact culprit lesion after reperfusion therapy. Karha et al. considered a lesion as proximal if it was located before the first diagonal branch and mid if located between the first and the second diagonal. All lesions distal to the second diagonal branch were considered distal. In contrast to our study, their definition did not take into account the size of the side branch. Probably, small side branches are without major electrophysiologic or clinical importance. Accordingly, the definition used by Karha et al. could classify a lesion distal to a minor first diagonal side branch as a mid-LAD occlusion, although the lesion was situated quite proximal in the artery with a large area of myocardium-at-risk. This highlights the difficulties often encountered when defining level of occlusion in different individuals with wide variations in coronary anatomy. Elsman et al. reported that proximal LAD-related infarcts treated with primary PCI were associated with higher short- and long-term mortality compared with distal LAD lesions [5]. In their single-center study from the mid-1990s, use of antithrombotic therapy, differed significantly from that in newer trials, like the DANAMI-2. Also, ischaemic time between onset of symptoms and first balloon inflation was not reported. In our study patients with acute STEMI early after the onset of symptoms were included. We hypothesize that the more complete and durable reperfusion offered by PCI in the DANAMI-2 trial, and the aggressive contemporary medical therapy used in secondary prevention, neutralized the negative prognostic effect of the proximality of the culprit lesion in LAD within the primary PCI treatment arm. Perhaps more surprisingly there was no difference in clinical outcome in the fibrinolysis treatment group between proximal and distal occlusion defined by ECG.

In the present study, analysis concerning level of occlusion in the LAD was restricted to patients with the preinfarction syndrome, that is, without pathological Q waves and/or inverted T waves. Including cases with different evolving stages of STEMI may result in loss of important information about the size and localization of the jeopardized ischemic myocardium. Not surprisingly, time to randomization and time to first balloon inflation was shorter in patients with the preinfarction syndrome compared to those with other acute anterior MI, mostly evolving MI with Q waves and/or negative T waves. As our results differ from previous reports, the prognostic significance of the level of occlusion in the LAD and different ECG subgroups in the modern era of acute STEMI treatment should be reassessed in future studies.

5. Conclusion

Our findings suggest that the presence of ST-elevation ≥ 0.5 mm either in lead aVL or any ST-elevation in aVR in

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association with precordial ST-segment elevation in at least two contiguous leads (including V_2, V_3 or V_4) is an ECG marker with good sensitivity, positive and negative predictive values for a culprit lesion proximal to a medium-sized or large diagonal side branch. ECG or angiographic signs of a proximal lesion in the LAD was not associated with worse clinical outcome at 30 day and 2.7 year follow-up. The presence of ST-segment elevation in all inferior leads makes it unreliable to predict the level of obstruction in patients with acute anterior wall MI.

6. Study limitations

There are some limitations to this study. It was not originally planned as part of the DANAMI-2 study. As the ECG investigators were totally blinded to angiographic findings and clinical data of the patients and the number of patients was large, the post-hoc nature of the study should not have significant impact on the results.

Introducing markers of vessel size and more detailed information about the lesion in respect to septal and diagonal side branches could have improved the results of the statistical analysis concerning level of occlusion. It must be appreciated, though, that coronary anatomy shows big variations between individuals. Excluding patients with multivessel disease and well developed coronary collateral circulation could have improved the results, but at the same time weakened the applicability of our results to everyday clinical practice.

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