KJELL NIKUS

12-lead Electrocardiogram in Acute Coronary Syndrome

Association with Coronary Angiography Findings and Outcome

ACADEMIC DISSERTATION
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for public discussion in the Main Auditorium of Building M,
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To my family

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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 Nikus KC, Eskola MJ, Virtanen VK, Vikman S, Niemelä KO, Huhtala H, Sclarovsky S (2004). ST-Depression with Negative T Waves in Leads V_4-V_5 - A Marker of Severe Coronary Artery Disease in Non-ST Elevation Acute Coronary Syndrome: A Prospective Study of Angina at Rest, with Troponin, Clinical, Electrocardiographic, and Angiographic Correlation. Ann Noninvasive Electrocardiol 9:207-214.

II Nikus KC, Eskola MJ, Virtanen VK, Harju J, Huhtala H, Mikkelsson J, Karhunen PJ, Niemelä KO (2007). Mortality of patients with acute coronary syndromes still remains high: A follow-up study of 1188 consecutive patients admitted to a university hospital. Ann Med 39:63-71.

III Nikus KC, Sclarovsky S, Huhtala H, Niemelä K, Karhunen P, Eskola MJ (2012). Electrocardiographic presentation of global ischemia in acute coronary syndrome predicts poor outcome. Ann Med 44:494-502.

IV Nikus K, Järvinen O, Sclarovsky S, Huhtala H, Tarkka M, Eskola M (2011): Electrocardiographic presentation of left main disease in patients undergoing urgent or emergent coronary artery bypass grafting. Postgrad Med 123:42-48.

ABBREVIATIONS

ACS	acute coronary syndrome
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
AMI	acute myocardial infarction
BARI	Bypass Angioplasty Revascularization Investigation
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI	95% confidence interval
CSI	circumferential subendocardial ischemia
ECG	electrocardiogram
ESSENCE	The Enoxaparin in Non-Q-Wave Coronary Events
FRISC	Fragmin during Instability in Coronary Artery Disease
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries
HR	hazard ratio
IQR	inter-quartile range
LAD	left anterior descending coronary artery
LBBB	left bundle branch block
LCx	left circumflex coronary artery
LM	left main
LV	left ventricle
LVH	left ventricular hypertrophy
MI	myocardial infarction
NPV	negative predictive value
NSTE	non-ST-elevation
NSTE-ACS	non-ST elevation acute coronary syndrome
NSTEMI	non-ST-elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
PPV	positive predictive value
RCA	right coronary artery
RBBB	right bundle branch block
RR	relative risk
STE-ACS	ST-segment elevation acute coronary syndrome
STEMI	ST-segment elevation myocardial infarction
TACTICS	Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy
TIMI	Thrombolysis in Myocardial Infarction
UA	unstable angina pectoris

ABSTRACT

Based on randomized clinical trials, the mortality of acute coronary syndrome (ACS) has been regarded as relatively low. However, the prognosis of clinical presentations of ACS in unselected "real-life" patient cohorts has not been well-documented. The significance of the electrocardiogram (ECG) ST-segment depression in ACS has been the subject for debate for many decades. Studies indicate that various manifestations of ST/T changes may have significantly different prognostic implications. Widespread ST-segment depression in combination with lead aVR ST-segment elevation is a marker of an adverse outcome in patients with non-ST-elevation (NSTE-) ACS -- perhaps because this pattern is indicative of severe coronary artery disease (CAD), including left main coronary artery (LM) stenosis. However, the prognostic value of this circumferential subendocardial ischemia (CSI) ECG pattern has not yet been established.

The aims of the present study were to investigate the significance of ST-segment depression and T-wave changes in ACS, with respect to in-hospital prognosis, troponin levels and angiographic findings (**I**); evaluate the prognostic significance of the three different clinical entities of ACS in prospectively collected consecutive patients from a university hospital (**II**); study the distribution of various ECG patterns on admission in patients with ACS and define the prognostic value of these pre-defined ECG patterns (**III**); compare preoperative 12-lead ECG findings during anginal pain in patients with as well as without LM disease who underwent isolated urgent or emergent bypass surgery; and, finally, study the sensitivity, specificity and predictive values for the CSI ECG pattern to predict angiographic LM disease (**IV**).

The study populations for all four studies were collected at Tampere University Hospital. For Study **I**, 50 patients with ACS were collected prospectively and consecutively. Studies **II** and **III** comprised 1,188 ACS patients admitted to the emergency department of our hospital. The original study population for Study **IV** consisted of 1,131 patients who had isolated bypass surgery urgently or emergently.

Patients with ST-segment depression and inverted T waves maximally in leads V4-V5 had, significantly more often, LM or LM equivalent (proximal left anterior descending and circumflex) disease, 76 vs. 8% ($p<0.001$), heart failure; 40 vs. 4% ($p=0.005$) and higher in-hospital mortality; 24 vs. 0% ($p=0.02$), than patients with a positive T wave in the precordial lead with maximal ST-segment depression. The troponin levels did not differ significantly between the two groups (**I**).

For ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UA) categories, in-hospital mortality was 9.6, 13 and 2.6% ($p <0.001$) and mortality at a median follow-up of 10 months 19, 27 and 12% ($p<0.001$), respectively. In multivariate Cox regression analysis age, diabetes mellitus type 1, diuretic use at admission, serum creatinine level, lower systolic blood pressure, and STEMI and NSTEMI ACS categories were associated with higher mortality during follow-up (**II**).

To study the distribution of ECG changes and the prognostic value of the CSI ECG pattern, the patients (n=1,188) were classified into seven ECG categories: ST-segment elevation (29%), Q waves without ST-segment elevation (23%), left bundle branch block (6%), left ventricular hypertrophy (7%), CSI ECG (8%), other ST-segment depression and/or T-wave inversion (14%) and other findings (13%). The CSI ECG pattern predicted high rate (48%) of composite endpoints (mortality, re-infarction, UA, resuscitation or stroke) at 10 months' follow-up compared to the other ECG categories (36%) (Hazard ratio [HR] 1.78, 95% confidence interval [CI] 1.31-2.41, $p<0.001$). In multivariate analysis, the CSI ECG pattern was associated with a higher rate of composite endpoints at 10 months' follow-up (HR 1.40, 95% CI 1.02-1.91, $p=0.035$). The multivariate

analysis furthermore identified age, creatinine level and diabetes as independent predictors of prognosis (**III**).

In patients undergoing urgent or emergent bypass surgery, the CSI ECG pattern was found in 61 of 80 patients (76%) with and in 12 of 65 patients (19%) without angiographic LM disease. The sensitivity, specificity, positive and negative predictive values for LM disease in patients with the CSI ECG pattern were 76, 81, 84 and 74%, respectively. In multivariate analysis, the CSI ECG pattern was strongly associated with angiographic LM disease after adjusting for age, gender, diabetes, hypertension, and smoking (HR 16.0, 95% CI 6.5-39.5, $p<0.001$) (**IV**).

In conclusion, in an unselected patient cohort, short-term mortality of myocardial infarction patients, especially those classified as NSTEMI was high. In patients with NSTEMI, transient ST-segment depression and inverted T waves maximally in leads V4-V5 during anginal pain predicted LM or LM equivalent disease with high sensitivity and specificity. This CSI ECG pattern predicted an unfavourable outcome when compared to six other ECG patterns in patients with ACS. In addition, the CSI ECG pattern was strongly associated with angiographic LM disease in patients who underwent urgent or emergent coronary bypass grafting. In patients with ST-segment depression and positive T waves, there was high probability for single vessel disease and a better outcome.

TIIVISTELMÄ (Abstract in Finnish)

Satunnaistettujen kliinisten tutkimusten mukaan kuolleisuutta sepelvaltimotautikohtaukseen (ACS, acute coronary syndrome) on pidetty suhteellisen alhaisena. ACS:n eri kliinisten ilmenemismuotojen ennusteesta valikoitumattomassa potilasaineistossa on niukasti julkaistua tietoa. Sydänsähkökäyrän (EKG:n) ST-välin laskun merkityksestä on kiistelty vuosikymmenien ajan. Tutkimustulokset viittaavat siihen, että erilaisilla ST/T muutoksilla voi olla ennusteellista merkitystä. Laaja-alaiset ST-välin laskut yhdistettynä kytkennän aVR ST-välin nousuun viittaavat huonoon ennusteeseen ilman ST-välin nousuja ilmenevässä ACS:ssa (NSTE-ACS, non-ST elevation ACS) todennäköisesti siksi, että nämä muutokset viittaavat vasemman päärungon tautiin. Tämän sirkumferentiellin subendokardiaalisen iskemian (SSI) EKG-löydöksen ennusteellista merkitystä ei ole selvitetty.

Väitöskirjatyön tavoitteena oli tutkia ACS-potilaiden ST-välin laskujen ja T-aaltomuutosten merkitystä suhteessa sairaalahoitojakson ennusteeseen, troponiinitasoihin sekä sepelvaltimoiden varjoainekuvauslöydöksiin (**I**); arvioida ACS:n kliinisten ilmenemismuotojen ennusteellista merkitystä (**II**); tutkia ACS-potilaiden erilaisten EKG-ilmentymien esiintyvyyttä sairaalaan tulovaiheessa sekä arvioida näiden ennalta määritettyjen EKG-ryhmien ennustearvoa (**III**); verrata sepelvaltimoiden ohitusleikkauksella hoidettujen potilaiden EKG-muutoksia sen mukaan, oliko heillä vasemman sepelvaltimon päärungon tautia vai ei. Erityisesti tavoitteena oli tutkia ohitusleikkausta edeltäneen rintakipuoireen aikana rekisteröidyn EKG:n SSI-löydöksen sensitiivisyyttä, spesifisyyttä ja ennustearvoa vasemman sepelvaltimon päärunkotaudin suhteen (**IV**).

Kaikkien osatutkimusten potilaat kerättiin Tampereen Yliopistollisesta Sairaalasta. Tutkimus **I** käsitti 50 perättäistä NSTE-ACS potilasta. Tutkimusten **II** ja **III** perusjoukko koostui 1,181 potilaasta, jotka oli otettu sairaalaan ACS:n takia. Tutkimuksen **IV** alkuperäinen potilasaineisto

käsitti 1,131 potilasta, joille oli tehty sepelvaltimoiden ohitusleikkaus päivystyksenä tai kiireellisesti.

Verrattaessa kahta ryhmää toisiinsa (ryhmä A; suurin ST-välin lasku ja samanaikainen T-aallon negatiivisuus kytkennöissä V4-V5 sekä ryhmä B; suurimpaan rintakytkentöjen ST-välin laskuun liittyi T-aallon positiivisuus) todettiin, että päärunkotautia tai sen kanssa ekvivalenttia sepelvaltimotautia (vasemman eteen laskevan ja kiertävän haaran alkuosan ahtauma) ja sydämen vajaatoimintaa oli enemmän ryhmässä A kuin ryhmässä B (76 ja 8% [p<0.001] sekä 40 ja 4% [p=0.005], vastaavassa järjestyksessä). Sairaalakuolleisuus oli korkeampi ryhmässä A (24%) kuin ryhmässä B (0%) (p=0.02). Troponiiniarvot eivät eronneet ryhmien välillä (**I**).

ST-nousuinfarktin (STEMI, ST-elevation myocardial infarction), sydäninfarktin ilman ST-nousua (NSTEMI, non-ST-elevation myocardial infarction) ja epävakaan angina pectoriksen sairaalakuolleisuus oli 9.6, 13 ja 2.6% (p<0.001) sekä kuolleisuus 10 kuukauden seuranta-ajan kuluessa 19, 27 ja 12% (p<0.001), vastaavassa järjestyksessä. Monimuuttuja-analyysissä itsenäisiä riskitekijöitä seuranta-ajan kuolleisuuden suhteen olivat korkea ikä, tyyppi 1 diabetes, diureetin käyttö sairaalaan tullessa, kreatiniinitaso, matala systolinen verenpaine, STEMI ja NSTEMI (**II**).

Yleisin ACS-potilaan EKG-ilmentymä oli ST-välin nousu (29%) ja sitä seurasivat Q-aalto ilman ST-välin nousua (23%), vasen haarakatkos (6%), vasemman kammion hypertrofia (7%), SSI:n EKG-löydös (8%), muu ST-välin lasku ja/tai T-inversio (14%) sekä muut muutokset (13%). SSI:n EKG-löydös ennusti suurta määrää (48%) päätepahtumia (kuolleisuuden, uusintainfarktin, epävakaan angina pectoriksen, elvytyksen tai aivoverenkiertohäiriöiden yhdistelmä) 10 kuukauden seurannassa verrattuna muihin EKG-ilmentymiin (36%) (HR [hazard ratio] 1.78, 95% CI [luottamusväli] 1.31-2.41, p<0.001). Monimuuttuja-analyysissä SSI:n EKG-löydös yhdistyi suurempaan määrään yhdistelmäpäätetapahtumia 10 kuukauden seurannassa (HR 1.40, 95% CI 1.02-1.91, p=0.035). SSI:n EKG-löydöksen lisäksi korkea ikä, kreatiniinitaso ja diabetes olivat itsenäisiä ennustetekijöitä monimuuttuja-analyysissä (**III**).

SSI:n EKG-löydös todettiin 61/80 päivystykselliseen tai kiireelliseen ohitusleikkaukseen joutuneista potilaalla (76%), joilla sepelvaltimoiden varjoainekuvauksessa oli merkittävä vasemman päärungon ahtauma. Sama EKG-muutos todettiin vain 12/65 potilaalla (19%), joilla ei ollut päärunkotautia. SSI:n EKG-löydöksen sensitiivisyys, spesifisyys, positiivinen ja negatiivinen ennustearvo päärunkotaudin suhteen oli 76, 81, 84 ja 74%. Monimuuttuja-analyysissä tämä EKG-löydös yhdistyi vahvasti päärunkotautiin (HR 16.0, 95% CI 6.5-39.5, p<0.001) (**IV**).

Yhteenvetona: Sydäninfarktin ilman ST-nousua ilmenevässä muodossa lyhyen aikavälin kuolleisuus todettiin korkeaksi. Erityisen huono ennuste oli potilailla, joiden rintakivun aikana otetussa EKG:ssa oli ohimenevä ST-välin lasku ja T-aallon inversio maksimaalisena kytkennöissä V4-V5. Kyseinen SSI:n EKG-löydös ennusti päärunkotautia tai sen kanssa ekvivalenttia sepelvaltimotautia korkealla sensitiivisyydellä ja spesifisyydellä. Lisäksi mainitulla SSI:n EKG-muutoksella oli vahva yhteys varjoainekuvauksessa todettavaan päärunkotautiin potilailla, joille tehtiin päivystyksellinen tai kiireellinen sepelvaltimoiden ohitusleikkaus. Kun EKG-muutoksina olivat ST-välin lasku ja positiivinen T-aalto, potilaalla oli suurella todennäköisyydellä yhden suonen sepelvaltimotauti ja parempi ennuste.

INTRODUCTION

Myocardial ischemia can occur during two pathophysiologic processes: *decreased blood supply*, in which a coronary artery has been acutely occluded by a thrombus or vasospasm, or *increased myocardial demand* in which there has been acutely increased cardiac work by exercise or other stress in the presence of coronary artery disease (CAD). Patients with myocardial ischemia as a result of decreased supply typically present with two types of electrocardiogram (ECG) patterns: a) predominant ST-segment elevation acute coronary syndrome (STE-ACS), and are classified as having either "aborted myocardial infarction (MI)" or ST-elevation MI (STEMI) based on the presence or absence of biomarkers of myocardial necrosis; and b) patients without predominant ST-segment elevation on the 12-lead ECG - non-ST elevation ACS (NSTE-ACS) (Antman et al. 2004; Bassand et al. 2007). STE-ACS has homogeneous etiology of transmural ischemia typically caused by fibrin-rich (red) thrombus occluding the infarct-related artery, except in cases of cardiac spasm. NSTE-ACS has heterogeneous etiologies of predominantly subendocardial ischemia, frequently caused by a platelet-rich (white) thrombus (Mizuno et al. 1992).

The majority of patients presenting with a clinical syndrome compatible with STE-ACS progress into the evolving stages of STEMI, and a minority have aborted MI (Lamfers et al. 2003). Patients presenting with NSTE-ACS represent a wide spectrum of severity of CAD and, therefore, have major differences in the outcome. Urgent reperfusion with thrombolytic therapy has been proven to be beneficial only in patients presenting with ST-segment elevation, whereas in the general group without ST-segment elevation, including those with ST-segment depression, flat or negative T wave and even normal or unchanged ECG, it may be harmful (Braunwald et al. 2002). Moreover, studies have shown a superiority of an invasive strategy over a conservative one in high-risk patients with NSTE-ACS (Cannon et al. 2001a). Rapid risk stratification of patients with NSTE-ACS is crucial

for appropriate management of these patients and for targeting more potent and invasive therapies for higher-risk patients.

The ECG remains the most immediately accessible and widely used diagnostic tool for guiding emergent treatment strategies. The ECG recorded during acute myocardial ischemia is of diagnostic, therapeutic and prognostic significance. There is clearly a need to determine subgroups of patients having anatomically or functionally severe coronary obstruction based on standard 12-lead ECG interpretation. It was recently been pointed out that there are overlooked subgroups with NSTE-ACS who may potentially benefit from emergent reperfusion therapy (Hennings and Fesmire 2011).

When ischemia is confined primarily to the subendocardium, the overall ST vector typically faces the inner ventricular layer and the ventricular cavity such that the surface ECG leads show ST-segment depression. This subendocardial ischemic pattern is a frequent finding during spontaneous episodes of rest angina. In cases of severe extensive subendocardial ischemia, as in acute subtotal or even total occlusion of the left main coronary artery (LM), the injury vector may be seen as ST-segment depression in the majority of the ECG leads but as ST-segment elevation in lead aVR (Nikus et al. 2010).

Localization of subendocardial ischemia from the ECG changes is not as straight-forward as in the case of regional transmural ischemia due to total vessel occlusion. Reproducing subendocardial ischemia in animal models has proven difficult (Levine and Ford 1950). It is partly due to this that the ECG manifestations of subendocardial ischemia are not well-defined in the literature.

It is especially important to identify patients with severe CAD, including LM disease, since these are associated with high mortality, conceivably by means of non-invasive methods. Accordingly, ST-segment depression and lead aVR ST-segment elevation have been established as ECG markers of poor outcome in NSTE-ACS (Holmvang et al. 2003; Kaul et al. 2001; Savonitto et al. 2005; Taglieri et al. 2011). The ECG pattern with widespread ST-segment depression and

inverted T waves maximally in leads V4-V5 has been described by Sclarovsky as circumferential subendocardial ischemia (CSI) (Figure 1) (Sclarovsky 1999). The prognostic value of this ECG pattern of circumferential subendocardial or global ischemia in comparison with other ECG manifestations of ACS has not been studied.

The focus of this thesis was to study the association between the ECG pattern of CSI, angiography findings and patient outcome in NSTE-ACS, with the ultimate goal of finding a non-invasive method for recognizing LM disease.

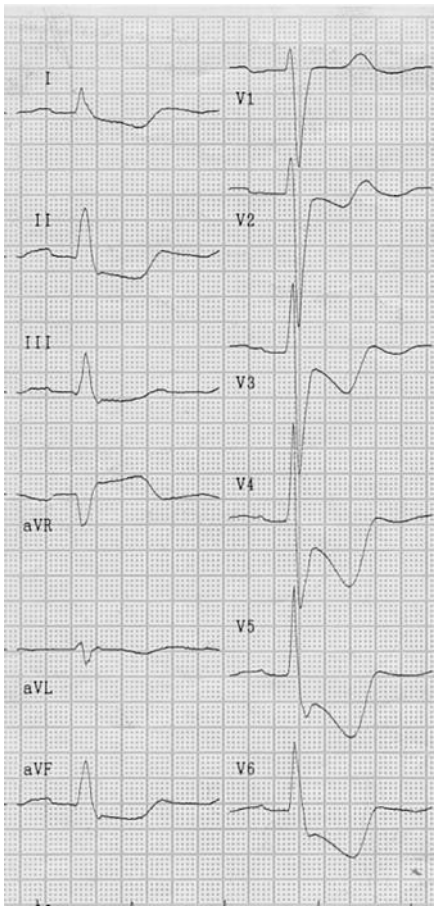

Figure 1. The ECG pattern with widespread ST-segment depression and inverted T waves maximally in leads V4-V5 has been described by Sclarovsky as circumferential subendocardial ischemia. There is ST-segment depression in leads I, II, III, aVF, V2-V6. Note also the ST-segment elevation in lead aVR.

REVIEW OF THE LITERATURE

1. Non-ST-elevation acute coronary syndrome

1.1 Definition

Myocardial ischemia is characterized by an imbalance between myocardial oxygen supply and demand. MI is defined as myocardial cell death due to prolonged ischemia. The condition is diagnosed when blood levels of biochemical markers of cell death are increased in the clinical setting of acute myocardial ischemia (Alpert et al. 2000). While patients with ongoing chest discomfort and persistent ST-segment elevation are classified as STE-ACS, NSTE-ACS patients are, in turn, classified as having either non-ST-segment elevation MI (NSTEMI) or unstable angina pectoris (UA), based on the presence or absence of biomarkers of myocardial necrosis (Antman et al. 2004). MI may occur with atypical symptoms or even without symptoms, being detectable only by the ECG, biomarkers or cardiac imaging (Thygesen et al. 2007).

The most common cause of NSTE-ACS is reduced myocardial perfusion that results from coronary artery narrowing caused by a nonocclusive thrombus that has developed on a disrupted atherosclerotic plaque (Freeman et al. 1989).

1.2 Distribution and incidence

The relative incidence of the ACS categories differs between study populations; this discrepancy may partly be explained by differences in the patient inclusion rate and criteria. The study by

Terkelsen et al from Denmark represents a "real-life" study population, where an Endpoints Committee determined whether the patients fulfilled established acute MI (AMI) criteria (Terkelsen et al. 2005). The authors claimed that a total cohort of MI patients from a chosen study region was identified. The study included 654 consecutive patients with AMI from 1999 to 2001. The study region had 139,000 inhabitants. The relative distribution of categories of MI was: 54% NSTEMI, 39% STEMI and 6% left bundle branch block (LBBB)-MI.

Registry studies rely on voluntarily reported cases from the participating centres. This could result in an overrepresentation of large MIs, which usually are STEMIs. The Global Registry of Acute Coronary Events (GRACE) registry included 31,982 patients with suspicion of ACS representing 25 countries from Asia, Europe, North and South America as well as Australia. According to final diagnosis, 9,557 patients (31%) had STEMI, 9,783 (32%) NSTEMI, and 8,037 (26%) UA. In addition, 2,453 (8%) patients had another cardiac diagnosis and 1,150 (4%) a noncardiac final diagnosis (Goodman et al. 2009). Hence, the relative distribution of ACS was 35% STEMI, 36% NSTEMI and 29% UA patients. In patients with AMI in the Swedish national registry (RIKS-HIA), there has been a considerable relative increase of patients with NSTEMI from 46 to 63% during 13 years of annual surveying, while there has been a dramatic decrease of STEMI from 45 to 29% during the same time period (http://www.ucr.uu.se/rikshia/). LBBB-MI represents ~8% of MIs. In RIKS-HIA, 14% of the patients with ACS had UA as the final diagnosis. A Spanish consecutive MI register from 6 hospitals found a relatively high incidence of STEMI of 60.3%, while 32.7% were classified as NSTEMI (Marrugat et al. 2004). Unclassified MI was present in 7% of the patients. Notably, patients aged 80 or older and patients with prior MI were excluded, which probably explains the low relative incidence of NSTEMI.

The Swedish registry reported ~19,600 AMIs in 2010, of these, ~5,100 were STEMIs. The amount of MIs corresponds to a total number of AMI of about 20.9 per 10,000 inhabitants. NSTE-

ACS accounts for approximately 2-2.5 million hospital admissions annually worldwide (Savonitto et al. 2005).

1.3 Prognosis

Mortality from coronary heart disease has declined over recent decades in most industrialized countries; however, coronary heart disease remains a leading cause of death and morbidity (Kattainen et al. 2006). NSTEMI and UA represent NSTE-ACS and are heterogeneous disorders in which patients have widely varying risks. The vast majority of events in NSTEMI patients occur in the first few days or weeks after the initial attack (Fox et al. 2006). The benefit of an invasive treatment strategy in NSTE-ACS is most evident in high-risk patients. In the Fast Revascularization during InStability in Coronary artery disease II (FRISC-II) trial, in patients with ST-segment depression, the invasive strategy reduced death/MI at 12 months from 18.2 to 12% (Relative risk [RR] 0.66, 95% confidence interval [CI] 0.50-0.88, p=0.004), while mortality was changed from 5.8 to 3.3% (p=0.050) (Diderholm et al. 2002).

1.3.1 Non-ST-elevation myocardial infarction

In most published studies, lower in-hospital mortality has been reported for NSTEMI than for STEMI. In a Spanish registry study (n=2,048), NSTEMI and STEMI 28-day case fatality was 3.0 and 5.3%, respectively (p=0.02) (Garcia-Garcia et al. 2011). However, the multivariate adjusted seven-year mortality for 28-day survivors was higher for NSTEMI than for STEMI (Hazard ratio [HR] 1.31, 95% CI 1.02-1.68, p=0.035), and patients with unclassified MI (pacemaker ECG and LBBB) presented the highest short- and long-term mortality (28-day mortality 11.8%, seven-year mortality 35.4%). At two-year follow-up in the Polish Registry of ACS, (STEMI [n=8,250]; NSTEMI [n=5,191]), NSTEMI was associated with a higher incidence of death (26.0 vs. 22.9%; HR 1.09, 95% CI 1.02-1.17, p<0.0001); a higher incidence of reinfarction (10.1 vs. 8.2%; HR 1.23,

95% CI 1.09-1.37, p=0.0005), stroke (3.3 vs. 2.3%; HR 1.43, 95% CI 1.16-1.76, p=0.007), coronary artery bypass grafting (CABG) (10.4 vs. 8.3%; HR 1.25, 95% CI 1.12.-1.40, p<0.001) and a lower rate of percutaneous coronary intervention (PCI) (12.5 vs. 14.2%; HR 0.86, 95% CI 0.78-0.94, p=0.002) compared with STEMI (Polonski et al. 2011). Adjustments for baseline characteristics and treatment strategy (invasive vs. non-invasive) reversed the HR for mortality and eliminated the difference in MI and stroke. The adjusted HR for NSTEMI mortality was 0.76 (95% CI 0.71-0.83, p<0.0001). Hence, the unadjusted long-term prognosis was worse in NSTEMI, but after adjustment for the baseline characteristics and treatment strategy, the long-term prognosis was worse in STEMI. Patients with MI treated invasively showed more favorable clinical characteristics and received guideline-recommended therapy more often than patients who did not undergo invasive treatment.

Lower mortality figures for NSTE-ACS have been reported in randomized clinical trials and in registry studies than in "real life" cohorts of consecutive patients. In-hospital (seven-day) mortality in A to Z, a large randomized study comparing enoxaparin with unfractionated heparin in patients with NSTE-ACS, was only 1% (de Lemos et al. 2004); three-quarters of the patients were classified as MI. Median age was only 61, indicating selective patient inclusion. In a study of four registries, where 13,556 NSTE-ACS patients were collected between 1999 and 2008, in-hospital mortality was only 0.7% in patients enrolled in clinical trials, while non-participants had 2.1% mortality (p=0.001) (Hutchinson-Jaffe et al. 2010). The median age was 65 and 68 years in enrolled and non-enrolled patients, respectively. These numbers are in strong contrast with the results from the "real-life" study from Denmark, where in-hospital mortality for NSTEMI patients was 13.3% (95% CI 9.7-16.8) (Terkelsen et al. 2005). In the Danish study, one-year NSTEMI mortality was 30.5% (95% CI 26.0-35.6), while STEMI mortality was 10.9% (95% CI 7.0-14.7) and 20.5% (95% CI 16.1-26.0) in hospital and at one year, respectively.

However, there are differences between registry studies. In the National Registry of Myocardial Infarction 2-4 observational studies (n=255,256), in-hospital mortality rates were 15.8% for patients with ST-segment depression and 15.5% for those with ST-segment elevation or LBBB (Pitta et al. 2005). Also, the in-hospital cardiac event rates were similar in patients with ST-segment depression (33%) and in those with ST-segment elevation or LBBB (34%). Patients who had ST-segment depression were, on average, 5.1 years older and were more likely to have a history of long-term illness. They were also less likely to receive aspirin, beta-adrenergic receptor blockers, antiplatelets, antithrombins, intravenous nitroclygerin, heparin, and glycoprotein IIb/IIIa inhibitors than were patients with ST-segment elevation or LBBB.

1.3.2 Unstable angina pectoris

UA mortality is rarely reported in published studies, because these patients are usually studied together with NSTEMI patients as NSTE-ACS. The 28 day mortality rates of 2,681 patients with UA in 5 Spanish registries were 2.2% in men (mean age 63.6 y) and 3.5% in women (mean age 68.6 y) (Marrugat et al. 2004).

2. Distribution of ECG changes at admission in acute coronary syndrome

ST-segment depression is a relatively frequent finding in ACS patients, as almost 40% of a total of over 55,000 patients in a large registry presented this ECG abnormality (Ryan et al. 2005). In a prospective analysis of consecutive admissions for ACS in a single coronary care unit, 792 (62%) patients had a diagnosis of UA or NSTEMI, 445 (35%) had STE-ACS, and 37 (3%) had paced electrical rhythm ACS (Teixeira et al. 2010). Of the patients without persistent ST-segment elevation or paced rhythm, normal ECG was the most frequent ECG finding, followed by T-wave

inversion and ST-segment depression (Figure 2). The authors did not report the ECG findings in 55 patients (7%). In NSTE-ACS, a normal ECG was an early marker for good prognosis.

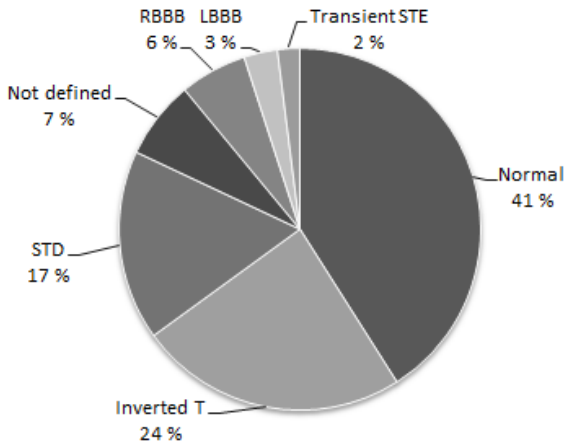

Figure 2. The distribution of ECG changes in consecutive NSTE-ACS patients (n=792). STD=ST-segment depression; STE=ST-segment elevation; RBBB=right bundle branch block; LBBB=left bundle branch block. Modified from the study by Teixeira R et al (2010).

In a national registry of 1,475 patients hospitalized in the cardiology clinics or the emergency units of six major general hospitals with ACS in Greece, 595 (34%) had ST-segment elevation and 392 (24%) had ≥1 mm ST-segment depression or T-wave inversion, while 488 patients (32%) had non-diagnostic ECG abnormalities (old LBBB, atrial fibrillation, paced rhythm, ventricular or supraventricular tachycardia, advanced atrioventricular block) (Pitsavos et al. 2008).

In AMI patients with normal creatine kinase MB-levels, the distribution of ECG changes was: T-wave inversion 25 patients (50%), ST-segment elevation in 16 (32%), ST-segment depression in 6 (12%), normal ECG in 11 (22%), right bundle branch block (RBBB) in 8 (16%), LBBB in 2 (4%), and left anterior hemiblock in 2 (4%) patients (Gruberg et al. 2008).

Out of 250 consecutive patients admitted for evaluation of chest pain, 49 (19.6%) were subsequently diagnosed with an AMI (Challa et al. 2007). Of the remaining 201 patients, 39 were diagnosed with a definite or probable cardiovascular cause of their chest pain. Of the 75 patients presenting with normal ECG, 1 (1.3%) was subsequently diagnosed with a MI by Troponin I elevation alone. Of the 55 patients presenting with abnormal ECGs but no clear evidence of

ischemia (i.e., LBBB, RBBB, left anterior hemiblock), 2 (3.6%) were diagnosed with MI. Of the 48 patients presenting with abnormal ECGs questionable for ischemia (nonspecific ST- and T-wave changes that were not clearly ST-segment elevation or depression), 7 (14.6%) were diagnosed with an MI. Of the 72 patients who presented with abnormal ECGs showing ischemia (acute ST-segment elevation and/or depression), 39 (54.2%) were shown to have evidence for MI.

Taken together, the distribution of ECG changes at admission in ACS differs considerably between individual studies.

3. Coronary anatomy

3.1 Coronary artery dominance

The coronary artery circulation is composed of two principal arteries, the left and the right coronary artery (RCA), arising from the aorta (Figures 3-4). The two principal coronary arteries and their larger branches are arranged on the surface of the heart (extramural vessels), and give rise to branches that penetrate the myocardium (intramural vessels). The major epicardial vessels and their second- and third-order branches can be visualized by coronary angiography. The network of smaller intramyocardial branches is generally not seen.

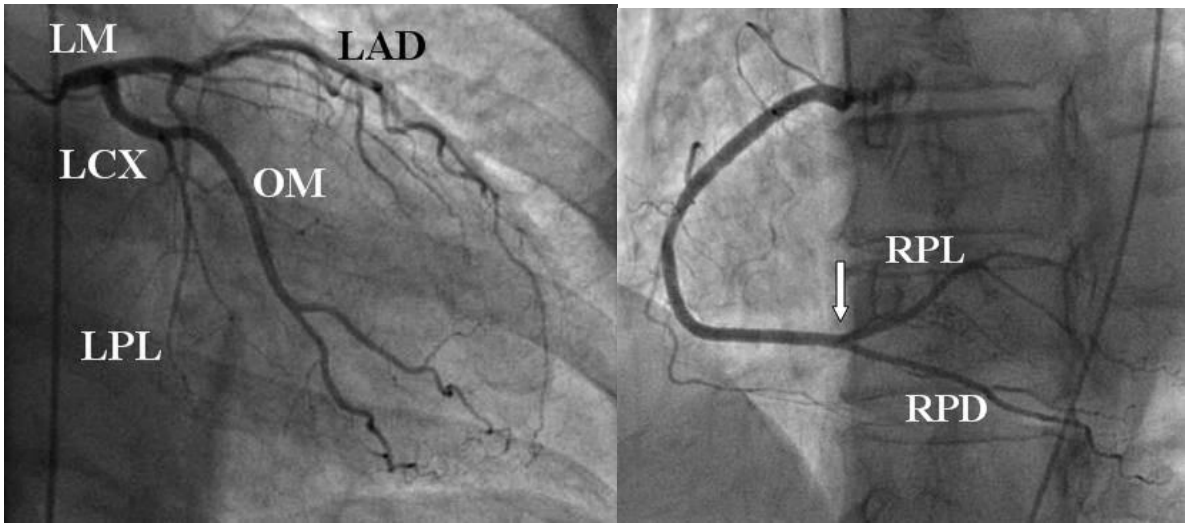

Figure 3. Coronary angiography images of the left (left) and right (right) coronary arteries with their branches. The white arrow indicates the crux cordis, where the right coronary artery divides into its 2 main distal branches. LM=left main coronary artery; LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery; OM=obtuse marginal; LPL=left posterolateral; RPL=right posterolateral; RPD=right posterior descending.

Variations in the branching pattern are extremely common in the human heart. According to the Bypass Angioplasty Revascularization Investigation (BARI) classification, the RCA is predominant in ~85% of individuals, providing the posterior descending (posterior interventricular) branch and at least one posterolateral branch (Figure 3) (Bari protocol 1991). In 7-8% of individuals, the coronary circulation is left-dominant; the posterolateral, the posterior descending, and the atrioventricular nodal branches are all supplied by the terminal portion of the left circumflex coronary artery (LCx) (Figure 4). In another 7-8% of hearts, there is a codominant or balanced system, in which the RCA gives rise to the posterior descending branch, and the LCx gives rise to all the posterolateral branches and, in some individuals, also to a parallel posterior descending branch that supplies part of the interventricular septum.

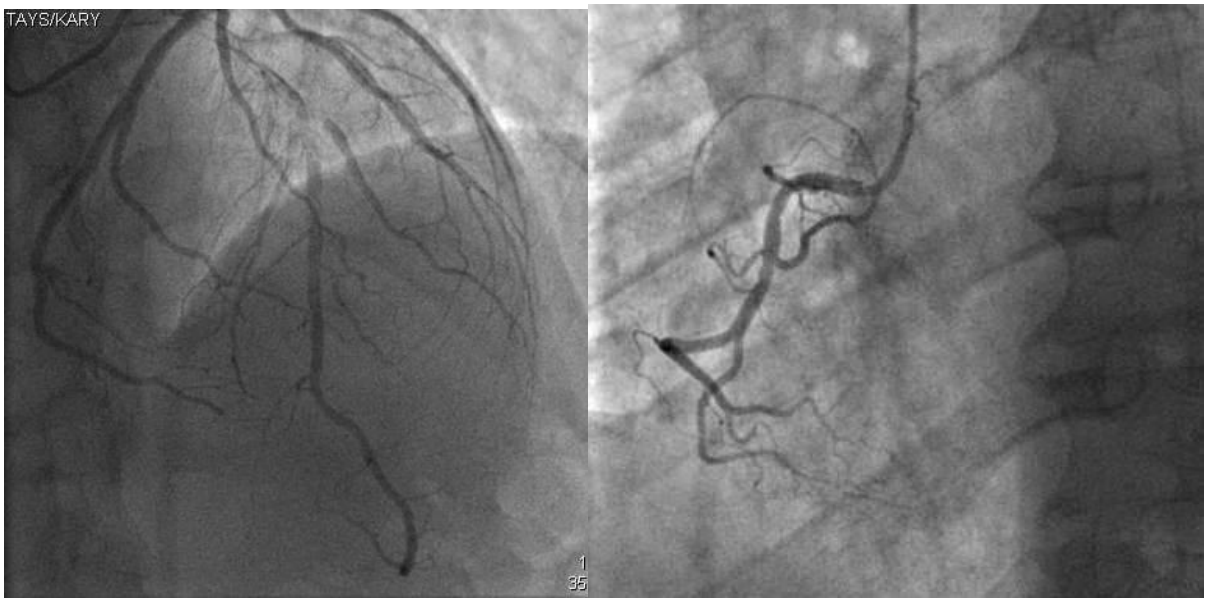

Figure 4. The coronary anatomy in left-dominant circulation. The left coronary artery (left) shows large distal branches, while the right coronary artery (right) is small (non-dominant).

3.2 Left coronary artery

The LM refers to the proximal segment of the left coronary artery that arises from the midportion of the left aortic sinus to its bifurcation into the left anterior descending coronary artery (LAD) and the LCx (Figure 3). The LM consists of three parts: the ostium, trunk and distal part. The most common site of LM stenosis is the midportion or at the bifurcation (Ladich E et al. 2006) (Figure 7). The LM is a relatively large-caliber vessel, supplying more than 75% of the coronary blood flow to the left ventricle (LV) (Ladich E et al. 2006).

The LAD is a direct continuation of the main trunk. One or more diagonal branches arise from the LAD, subtending the anterolateral part of the LV. The LAD also gives rise to ~10 septal branches. The LCx arises from the LM, and gives off branches to the upper lateral LV wall and the left atrium. The left obtuse branches arise at a right or an acute angle from the LCx, and descend vertically toward the apex of the heart. In ~1/3 individuals, the left coronary artery trifurcates; the intermediate branch (ramus intermedius) comes off between the LAD and the LCx (Baroldi and Scomazzoni 1967). The direct origin of the LAD and the LCx by separate ostia from the aorta without a LM is present in about 1% of individuals (Schlesinger 1940).

3.3 Right coronary artery

The RCA usually gives rise to a large branch, the right acute marginal branch, along the acute margin of the heart. In most individuals (right dominance), the RCA gives off the posterolateral and posterior descending branches at the crux cordis (Figure 3). The atrio-ventricular nodal branch arises from the posterolateral branch. The most proximal side branch of the RCA, the conus branch, subtends the right part of the interventricular septum to a varying extent. In about 50% of individuals, the conus branch takes off directly from the aorta, either through a separate ostium (2/3) or through a common ostium with the RCA (1/3). The branch to the sinus node arises from the proximal RCA in the majority of individuals. In about 40% of human hearts, the sinus node is supplied by a branch arising within the first few millimeters of the course of the LCx (James 1960; Nikus 2011).

3.4 Coronary collateral flow

After total or near-total occlusion of a coronary artery, perfusion of ischemic myocardium occurs through collaterals, which are vascular channels that interconnect epicardial coronary arteries (Figure 5). Previously occluded vessel branches are usually manifested as truncated stumps on angiography. The part of the vessel distal to the occlusion is frequently filled late in the contrast injection by antegrade ("bridging") collaterals or collaterals that originate from the same or an adjacent vessel. In fresh total occlusions, typically represented by STEMI, no collateral flow may be evident from coronary angiography. Functioning collaterals maintain myocardial viability, but are not as effective as the native vessel for oxygen distribution. Some grade of effort angina is typical for patients with occluded coronary arteries and collateral flow. The presence of collaterals modifies the ECG changes seen in ACS patients (Zhang et al. 2010).

Collateral circulation is classed into four grades according to the grading system of Rentrop et al. (Rentrop et al. 1985). Briefly, grade 0 is no collateral opacification, grade 1 filling of side branches, grade 2 partial and grade 3 complete filling of the main branch by collateral vessels.

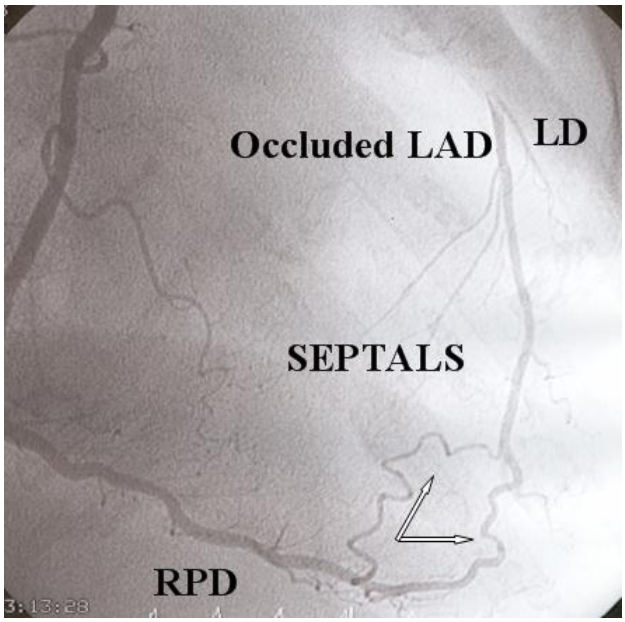

Figure 5. Well-developed (Rentrop Grade 3) collaterals (arrows) from the right coronary artery to the occluded left anterior descending coronary artery (LAD). RPD=right posterior descending; LD=left diagonal.

4. Severe coronary artery disease

4.1 Definition of significant coronary obstruction

A significant coronary obstruction is defined as 50% or more angiographic diameter stenosis in one or more of the epicardial coronary arteries, corresponding to a 75% or more reduction of the cross-sectional area (Figure 6) (Arnett et al. 1979). In general, though, defining CAD severity is rather complex. Acute occlusion even of a small coronary artery may be life-threatening, due to the electrical instability with the possibility of ventricular fibrillation generated by myocardial ischemia. There are also limitations with coronary angiography; in contrast to its topographical precision, the method is limited in gauging the functional repercussions of coronary stenosis. Especially in patients with angiographically dubious stenoses, ancillary diagnostic methods, like fractional flow reserve measurement may be useful (de Bruyne B and Sarma J 2008).

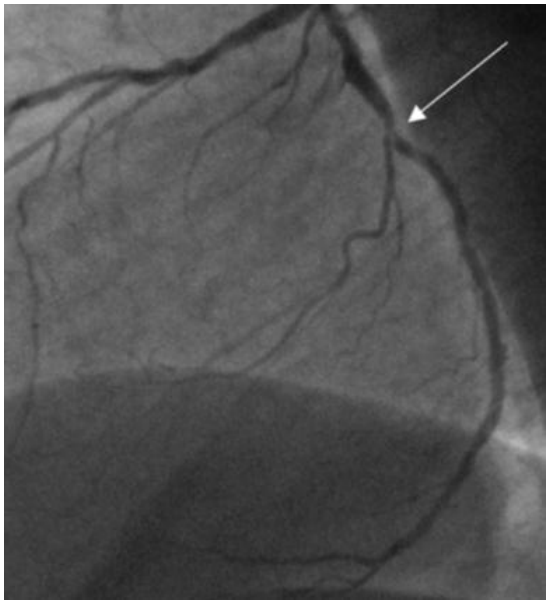

Figure 6. The coronary angiography shows a significant stenosis (>50% of the vessel diameter) of the left circumflex coronary artery at the level of an obtuse marginal side branch.

4.2 Anatomical classification

Based on disease severity, obstructive CAD is classified as single, double or triple vessel disease. Stenoses less than 50% are considered as non-symptom generating, except in cases with dynamic obstruction. However, there may be large differences in disease severity within the patient groups with single, double or triple vessel disease, depending on the level of the stenosis and whether there is main vessel or side branch disease, or diffuse coronary artery disease. LM stenosis is encountered as an isolated entity or in combination with a varying degree of concomitant lesions within the coronary tree. In unprotected LM disease, there are no bypass grafts feeding the branches of the left coronary artery.

Of patients enrolled in the Thrombolysis in Myocardial Infarction (TIMI) IIIB study with UA and NSTEMI, 15% had >60% stenosis of 3 vessels, 30% had double vessel, and 40% single vessel disease; 5-10% had LM stenosis greater than 50% (TIMI IIIB 1994). Similar findings of the distribution of CAD have been reported from registries (Cannon et al. 1997; Scirica et al. 1999).

The culprit lesion in UA typically exhibits an excentric stenosis with scalloped or overhanging edges and a narrow neck (TIMI IIIA 1993).

4.3. Left main disease and its equivalent

Significant LM disease (Figure 7) is present in 4-10% of patients undergoing diagnostic coronary angiography, but total occlusion is encountered in only 0.04 to 0.42% of cases (de Feyter and Serruys 1984). Right-dominance and well-developed collateral channels are almost exclusively present (Topaz et al. 1991), when total occlusion is present. LM disease is usually accompanied by significant disease elsewhere in the coronary tree, which usually leads to symptoms and presentation before complete obstruction occurs (Bulkley and Roberts 1976). LV ejection fraction may be normal in patients with good collateral flow from the RCA and no previous MI (Goldberg et al. 1978). Significant obstruction of both the proximal segments of the LAD and LCx is defined as LM equivalent disease (Figure 7).

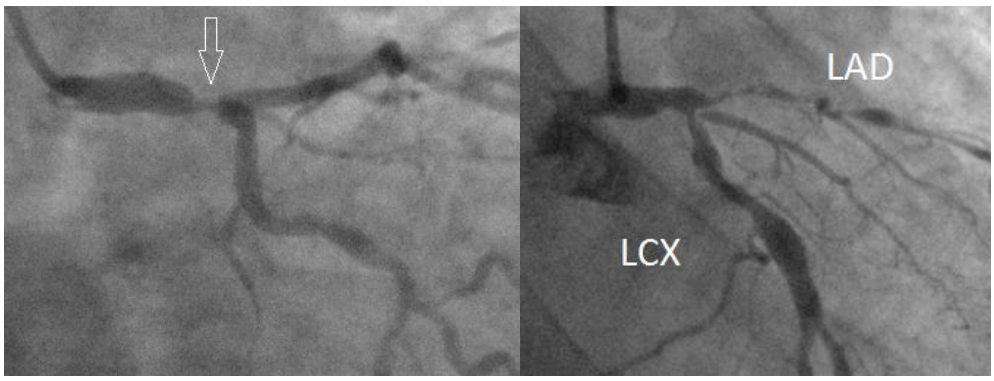

Figure 7. Coronary angiography findings in isolated stenosis (arrow) of the distal left main coronary artery (left) and in left main equivalent disease (right). LAD=left anterior descending coronary artery; LCX=left circumflex coronary artery.

Autopsy of patients diagnosed as UA (before the introduction of troponins) revealed a high proportion of LM segments with severe luminal narrowing (Roberts and Virmani 1979). Practically all the individuals (n=22) had at least 50% narrowing of the LM and >40% had >75% narrowing. In contrast, in patients with healed infarcts who died of CAD (Virmani and Roberts 1980), and in

those who died from unrelated causes (Virmani and Roberts 1981), there were no LM segments with severe disease. In a separate study of 152 hearts from patients dying predominantly from CAD, 94% of hearts with LMs demonstrating >75% area luminal narrowing also demonstrated critical stenosis of each of the other 3 epicardial coronary arteries (Bulkley and Roberts 1976). These data indicate that severe LM disease generally results in unstable coronary syndrome and sudden death at a relatively early age, and that patients surviving MI with healed transmural infarcts rarely have critical stenosis of the LM (Ladich E et al. 2006). This inference is corroborated by another study of sudden coronary death in patients younger than 30 years (Virmani et al. 1983). In this study, as many as 50% of the patients had critical narrowing of the LM, while in 9 of the 48 individuals, the LM was the site of thrombosis.

4.4 Scoring systems

Scoring systems have been developed to more specifically characterize the coronary vasculature with respect to the number of lesions and their functional impact, location and complexity. The "Leaman score" is based on severity of luminal diameter narrowing and weighed according to the usual blood flow to the LV in each vessel or vessel segment (Leaman et al. 1981). In a right dominant system, the RCA supplies 16% and the left coronary artery 84% of the blood to the LV. This 84% is normally directed for 66% to the LAD and for 33% into the LCx. Thus, the LM supplies approximately 5 times, the LAD approximately 3.5 times and the LCx approximately 1.5 times as much blood as the RCA to the LV.

Recently, the Syntax score was developed as an angiographic grading tool (Sianos et al. 2005). The Syntax score takes into consideration coronary artery dominance, the total number of lesions, vessel diameter and lesion complexity, like presence of bifurcation lesions.

4.5 Prognosis

Lesion severity as expressed by coronary angiography will affect the outcome in NSTE-ACS.

4.5.1 Single, double and triple vessel disease

In the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial, single, double and triple vessel disease was present in 18.5, 28.1 and 44.2% of the patients, respectively (n=6,921), when the presence of CAD was defined as a stenosis of at least 30% in a major epicardial vessel (Lansky et al. 2010). The composite ischemic event rates, defined as death, MI, or unplanned revascularization, were 4.7% in patients with no diseased vessels, 13.1% in those with 1 diseased vessel, 16.9% in those with 2 diseased vessels, and 22.1% in those with 3 diseased vessels. The number of diseased vessels and worst percent diameter stenosis were predictors of one-year composite ischemia. The authors found that baseline angiographic markers of disease burden, calcification, and lesion severity provided important added independent predictive value for 30-day and one-year ischemic outcomes, beyond the well-recognized clinical risk factors. The findings emphasized the prognostic importance of the diagnostic angiogram in the risk stratification of patients presenting with ACS.

4.5.2 Left main disease

In the majority of individuals, the LM supplies approximately 75% of the LV myocardial mass. In individuals with left-dominant coronary artery circulation, almost the entire LV myocardial mass may be supplied by the LM. Significant stenosis, both in stable CAD and ACS, places the patient at risk of life-threatening LV dysfunction and malignant arrhythmias. It is generally accepted that the long-term prognosis for patients with LM disease treated medically is poor, with three-year survival <50-75% (DeMots et al. 1977; Lim et al. 1975). The survival benefit of CABG compared with

contemporary medical therapy was first shown in the Veterans Administration trial (Takaro et al. 1976) and confirmed in subsequent studies (ECSS group 1980; Emond et al. 1994). In addition, in 912 patients with LM equivalent disease, defined as combined stenoses of ≥70% in the proximal LAD before the first septal perforator and proximal LCx before the first obtuse marginal branch, the 15-year cumulative survival estimates were 44% for the 630 patients in the surgical group and 31% for the 282 patients in the medical group (Caracciolo et al. 1995). Median survival in the surgical group was 13.1 years (95% CI 12.7 to 14.1 years) compared with only 6.2 years (95% CI 4.8 to 7.9 years) in the medical group (difference, 6.9 years; $p<0.0001$). However, CABG did not significantly prolong median survival in patient subgroups with normal LV systolic function, even if a significant RCA stenosis (≥70%) also was present.

Recent studies have reported that PCI is also feasible and effective in LM disease (Seung et al. 2008; Silvestri et al. 2000). However, NSTE-ACS due to critical LM stenosis is associated with high morbidity even after successful PCI. In a study of clinical outcomes after PCI for ACS in unprotected LM disease (n=134), cardiac death, MI, or repeat revascularization were observed in 19% of the patients presenting with NSTEMI or UA (Puricel et al. 2011). All-cause mortality at 6 months was 6%. In a registry study of patients with unprotected LM disease, PCI was performed in 1,102 and CABG in 1,138 patients (Min et al. 2010). ACS was an independent predictor of all-cause mortality and target vessel revascularization in the overall population (HR 1.63 [1.11-2.39], p=0.012). In multivariate Cox regression analysis, ACS was a predictor of target vessel revascularization, but not mortality.

In a PCI registry from 80 centres in Germany from 80 hospitals (n=9,422 patients) treated with primary PCI, 4.5% of the patients, in whom a pre-procedure ECG was available for analysis, presented with ST-segment depression (Zeymer et al. 2004). Of the 9,422 registry patients, 1,333 (14.2%) patients were in cardiogenic shock. The infarct related artery was the LM in 6.0%. In-hospital mortality in the patients with LM stenosis was 81.3% (n=80). The LM as infarct-related

artery proved to be an independent predictor of in-hospital mortality (odds ratio [OR] 8.8, 95% CI 4.4–17.6).

In a multicentre, retrospective, observational study (n=1,101) of patients with unprotected LM stenosis treated with drug-eluting stents, 611 patients presented with ACS and 490 had stable CAD (Palmerini et al. 2010). During the two-year follow-up, the adjusted HR of cardiac mortality and MI of patients with ACS versus stable patients was 2.42 (95% CI 1.37 to 4.28, p=0.002). Patients with stable coronary disease had the lowest risk, patients with UA an intermediate risk, and patients with STEMI the highest risk.

In a study of 1,146 patients treated for unprotected LM disease, the Syntax score showed differential treatment effects of PCI with drug-eluting stenting and CABG (Park et al. 2011). Patients with less severe angiographic disease tended to have better outcome with PCI (five-year risk for death 6.1% with PCI vs. 16.2% for CABG, HR 0.52, 95% CI 0.21 to 1.28, p=0.15), while in those with more complex disease, patients having CABG had lower mortality. The differences were not statistically significant.

Palmerini et al performed Syntax scoring of 2,627 patients with NSTE-ACS, who underwent PCI (Palmerini et al. 2011). The patients were stratified according to tertiles of the score. Among patients in the first, second and third score tertiles, the one-year rates of mortality were 1.5, 1.6 and 4%, respectively (p=0.0005). The Syntax score proved to be an independent predictor of one-year death (HR 1.04, 95% CI 1.01 to 1.07, p=0.005). LM disease is a high weighing factor in the Syntax scoring system.

4.5.3 Left main disease and cardiogenic shock

Acute total occlusion of the LM is an uncommon clinical emergency that results in cardiogenic shock, a highly morbid clinical entity known as LM shock syndrome (Quigley et al. 1993). Emergency reperfusion with PCI or CABG, under stabilizing measures such as insertion of an intra-

aortic balloon pump, is the primary goal in patients with LM shock syndrome. Still, the mortality rate remains high, especially in case of scarce or total absence of collateralization between the RCA and the left coronary system. In 25 consecutive AMI patients, who presented with LM shock, an initial TIMI grade 0 flow was noted on the emergent coronary angiography among 56% of the patients (Yamane et al. 2005). After primary stenting with bare metal stents for the unprotected LM lesion, TIMI grade 3 flow was obtained among 84%. 30-day mortality was 32%, while one patient underwent emergent CABG for subacute stent thrombosis and three patients required elective CABG for residual disease during admission. Major adverse cardiac events (death, re-infarction, stroke, or target vessel revascularization) occurred in 68% (17/25) over a 12-month follow-up, including 40% of mortality.

5. Pathophysiology of ECG changes in non-ST elevation acute coronary syndrome

5.1 ST segment

5.1.1 Biochemical changes during myocardial ischemia

In coronary artery occlusion, oxygen tension within the myocardium falls to almost zero within a minute after complete cessation of blood flow. The ischemic myocardial cells consume all the available oxygen within a few minutes after the myocardium loses its blood supply; as a result, oxidative phosphorylation comes to a complete halt. The large amounts of phosphate released from hydrolysis of adenosine triphosphate in the ischemic heart cause calcium to be trapped within the sarcoplasmic reticulum. Phosphate pours out into the extracellular space, and to maintain electrical neutrality, these anions are accompanied by potassium, the major intracellular cation. This causes a large potassium efflux, which results in depolarization of the ischemic myocardial cells (Katz

2006). Myocardial cell death begins 15 to 40 minutes after the heart's blood supply is cut off completely, and about 6 hours later, few viable cells remain in the ischemic region. This progression resembles a wave of necrosis that begins in the endocardium, where energy requirements are greatest, and spreads outward through the wall of the left ventricle toward the epicardium (Reimer et al 1977). The timetable depends on the level of myocardial protection.

Depolarization of ischemic myocardial cells establishes differences in resting potential that allow current to flow between the normally perfused and ischemic regions of the heart. These currents, called injury currents, cause diagnostic ST-segment shifts on the surface ECG that help to distinguish between subendocardial ischemia, which depresses the ST segment and transmural ischemia, which in turn results in ST-segment elevation.

5.1.2 ST-segment depression in subendocardial ischemia

Subendocardial ischemia causes ST-segment depression when a layer of perfused myocardium separates the partially depolarized endocardium from the epicardial surface of the heart. ST-segment depression is commonly seen in demand ischemia – for example, during exercise, because energy starvation is most severe in the endocardium, where energy demands are highest and blood supply most precarious. ST-segment depression is also seen in LV hypertrophy (LVH) even when the coronary arteries are normal, due to the vulnerability of the subendocardium to energy starvation. The vulnerability of the subendocardium of the LV to hypoxia may be caused by higher resistance to blood flow in the smaller, longer arterioles in that region. The work produced by the subendocardial myocytes of the LV is greater than that of the myocytes located in the epicardium because of the unique anatomic configuration of the ventricles (Hurst 2007).

Sudden obstruction of the LM or its equivalent produces extensive myocardial ischemia involving almost all the LV. In dogs with normal hearts, inducing acute global myocardial ischemia

by reducing total coronary blood flow mechanically resulted in a significant rise in the LV end-diastolic pressure (Palacios et al. 1976). In another experiment with dogs, changes in diastolic mechanisms indicating loss of LV chamber compliance were observed with hydraulic constriction of the LM, which resulted in a 54% reduction in mean LV subendocardial blood flow. The reduction in coronary flow in the subendocardium of the LV shifts the electrical vector from the epicardium towards the subendocardium (Guyton et al. 1977). Magnetic resonance imaging enables detection of subendocardial ischemia during stress tests (Cheung and Chan 2011). Even diffuse subendocardial ischemia in patients with multivessel disease can be detected (Sakuma et al. 2005). So far, there are no studies using magnetic resonance imaging or other methods to localize or quantitize subendocardial ischemia during the acute stages of ACS.

5.1.3 ST-segment depression in subendocardial infarction

The exploration of pathophysiological mechanisms behind ST-segment depression has proved to be much more challenging than what has been the case with ST-segment elevation. Not much progress in this field was made during the first three to four decades after the pioneer ECG works of Einthoven. Kemball Price and Janes published the first case report of an isolated subendocardial infarction in 1943 (Kemball Price and Janes 1943). The ECG of the patient three days after an attack of chest pain lasting for two hours showed ST-segment depression and negative T waves in leads I and IV (a precordial lead). Twelve days later, these changes had nearly normalized. Autopsy showed severe multivessel disease and a large "sheet-like" subendocardial infarct.

During the 1940s, several investigators searched for the ECG manifestation of subendocardial injury. In 1940, Boyd and Scherf in experiments with dogs scarified the inner surface of the left ventricular apex with a sound introduced through the left auricle (Boyd and Scherf 1940). In some cases there was slight depression of the ST segment in leads II and III, and temporary reversal of the T wave in all three standard leads. In 1940, Kisch, Nahum and Hoff published their animal work

which had applied potassium chloride (Kisch et al. 1940). They could not find a specific ECG pattern for subendocardial injury. Other investigators encountered the same problems. Hence, Levine stated in 1950: “Nature, it seems, can fulfil the conditions of this experiment much more readily than can the physiologist” (Levine and Ford 1950).

Bayley described the correlation between ST-segment depression and subendocardial infarction in the mid-1940s (Bayley 1946). The author denominated this phenomenon as “injury-against-the-rule”. He postulated that a diffuse injury of the subendocardial lamina generates an injury axis with the direction of a line drawn from the centre of the injured region toward the centre of the involved ventricle. Bayley stated that the effect of injury-against-the-rule is produced whenever an injury is greater at the endocardial than the epicardial surface. Bayley also mentioned that a precordial lead taken with the exploring electrode superjacent to an injured region displays a downward displacement of the RS-T junction, and that the phenomenon of injury-against-the-rule appeared to be a common feature of ECG recordings during an attack of angina pectoris (Bayley 1946).

Also later on, the exploration of pathophysiological mechanisms behind ST-segment depression has proved much more challenging than for ST-segment elevation. It is difficult to devise a practical experiment which would produce only necrosis of the subendocardium without introducing factors which might complicate the interpretation of the ECG. On the other hand, the existence of isolated subendocardial injury has been shown in autopsy materials (Kemball Price and Janes 1943) and by cardiac magnetic resonance imaging (Wagner et al. 2003).

5.1.4 Reciprocal ST-segment depression

In STEMI, the ECG shows typical ST-segment elevation in leads facing the area of infarction, while ST-segment depression (termed reciprocal changes) is evident in leads anatomically opposite to the infarct site. In some cases, the reciprocal changes may be more evident than the small ST-segment elevations induced by coronary artery occlusion. In 107 consecutive patients with evolving

first acute inferior MI, 93 had ST-segment elevation of at least 1mm in at least one of the inferior leads II, III and aVF, and in 14 patients ST displacement did not reach 1 mm in any of these leads (Birnbaum et al. 1993). In both groups, reciprocal ST-segment depression occurred more frequently in lead aVL than in any other lead. Only three patients had no ST depression in aVL. In eight patients (7.5%), ST depression in aVL was the sole early ECG sign of the inferior MI.

5.2 T wave

The T wave expresses repolarization – the recovery of the heart. The T wave is sensitive to a variety of cardiac, extracardiac and physiologic abnormalities and interventions that alter repolarization in a nonuniform manner. In young healthy individuals, T-wave abnormalities have been reported with glucose ingestion, body positioning, deep inspiration, tachycardia, and obesity (Hiss et al. 1960). The genesis of the T wave on a cellular level has been a matter of debate through the entire 20th century (Hlaing et al. 2005). Longer action potential duration in the endocardium than in the epicardium is required to generate the normal upright T wave predominant in most of the twelve standard ECG leads. Transient tall and peaked T waves with lengthening of the QT interval are the first manifestations of acute myocardial ischemia in the case of sudden complete occlusion of an epicardial coronary artery, including coronary spasm (Smith 1918). On the other hand, inverted T waves in the early phases of STEMI have been associated with improved patient outcome related to an open infarct-related artery, restored myocardial blood flow, reappearance of the R wave and better left ventricular function (Agetsuma et al. 1996; Doevendans et al. 1995; Herz et al. 1999).

T-wave evolution in ischemic heart disease is not a marker of cell death, but instead caused by changes in the ion channels in regions of the heart that remain viable after an episode of severe ischemia (Katz 2006). In patients, in whom inverted T waves develop, episodes of re-ischemia often manifest as a change in the T-wave vector with positivization of the T waves, with or without ST-

segment elevation ("pseudonormalization"), in the ischemic region (Noble et al. 1976; Wasserburger and Corliss 1965; Zack et al. 1987).

Patients presenting with T-wave changes represent a heterogeneous group, and the underlying mechanism may not be easily appreciated from the ECG at presentation in an individual patient. However, the evidence points to the fact that like in demand ischemia during an exercise test in stable CAD, new, isolated, inverted T waves never appear in acute ongoing ischemia in ACS (Hayden et al. 2002). A number of clinical states in addition to ischemic heart disease – ranging from entirely benign presentations such as hyperventilation to life-threatening conditions (such as increased intracranial pressure) – may be associated with inverted T waves (Hayden et al. 2002).

6. ECG patterns during ischemia and correlation with coronary angiographic findings

6.1 Regional subendocardial ischemia

6.1.1 Definition

The term *regional subendocardial ischemia* for the phenomenon of ST-segment depression with positive T wave in the precordial leads was introduced by Sclarovsky in his textbook (Sclarovsky 1999) (Figures 8 and 9). According to Sclarovsky, the probable culprits in these cases are a subtotal occlusion of the LAD or total obstruction of the first diagonal branch or intermediate artery. A similar ECG pattern – ST-segment depression with positive T waves – may be present in regional transmural ischemia of the basal lateral (previously named as posterior) wall caused by total occlusion of the LCx or the RCA (mirror-image of ST-segment elevation and a negative T wave of reperfusion) (Bayes de Luna et al. 2006; Porter et al. 1998).

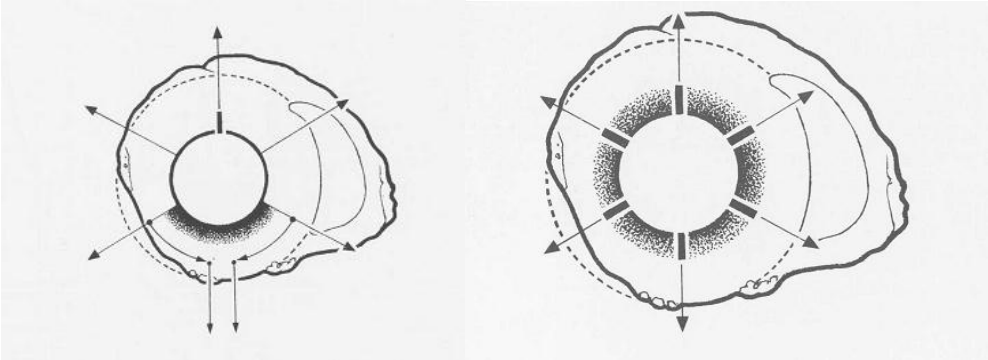

Figure 8. A schematic representation of the myocardium in short-axis in regional (left) and circumferential subendocardial ischemia (right). In regional ischemia, the area involved is localized, while in circumferential ischemia, there is 360° subendocardial involvement of the disease process. From Sclarovsky S. Electrocardiography of acute myocardial ischaemic syndromes (pages 94 and 96). Martin Dunitz Ltd 1999, London, UK, with permission.

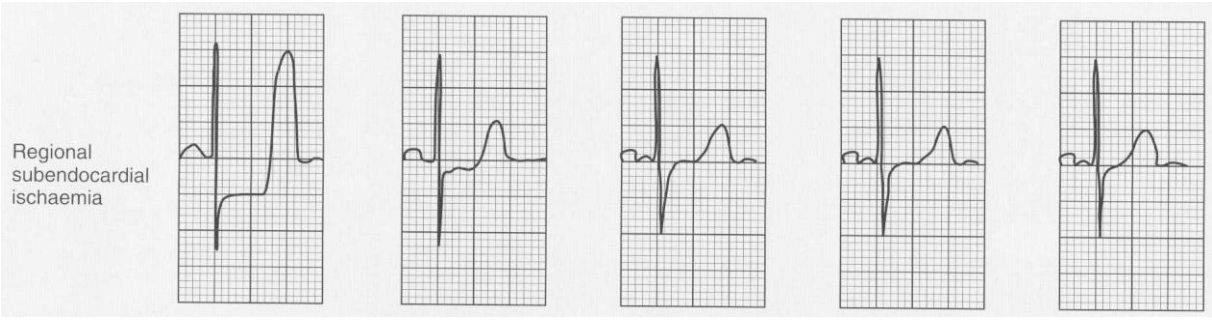

Figure 9. Schematic representation of regional subendocardial ischemia. The drawings show how the pattern changes from the initial phase with the most severe ischemia until normalization of the ECG. From Sclarovsky S. Electrocardiography of acute myocardial ischaemic syndromes (page 18). Martin Dunitz Ltd 1999, London, UK, with permission.

6.1.2 Study observations

Some ACS patients with one vessel disease, but without total coronary artery occlusion, present with rest angina, typically caused by plaque rupture or erosion with flow restriction. In these patients, myocardial ischemia is restricted to the myocardial segment supplied by one coronary artery or its side branch. In general, the ECG manifestations of regional subendocardial ischemia

are less well-defined than those of transmural ischemia. Characteristically, the number of leads with ST segment depression is usually <6 (Nikus et al. 2010). However, this observation is based more on clinical experience and case reports than on prospective studies of larger patient materials.

In the 1970s, it was shown that angiographically documented subtotal occlusion of the LAD produced ST-segment depression in leads V2-V4, while, during temporary total vessel occlusion, ST-segment elevation in the same leads was present (De Servi et al. 1979; Parodi et al. 1981). The investigators studied patients with angina pectoris at rest. Thallium-201 scintigraphic studies were performed during attacks of anginal pain at rest in a large number of patients. A regional reduction of myocardial perfusion was consistently documented. Regional reduction of myocardial perfusion was massive and transmural during episodes characterized by elevation of the ST segment, and corresponded well with the leads involved by ST-segment elevation (Maseri et al. 1976). Less massive, more diffuse deficits of thallium-201 uptake were observed during episodes characterized by ST-segment depression, a pattern compatible with diffuse subendocardial ischemia. The authors also noted episodes of peaking of T waves during these episodes, and coronary contrast injection at the same time showed poor distal coronary filling (Maseri et al. 1977; Maseri et al. 1978). Complete occlusion of the coronary artery was associated with ST-segment elevation.

Sclarovsky et al studied 32 ACS patients with rest angina without tachycardia, who had horizontal or downward-sloping ST-segment depression confined to the precordial leads (Sclarovsky et al. 1988a). ST-segment depression with positive peaked T waves was found in 21 patients and negative T waves in 11 patients. In the 21 patients with ECG signs of regional subendocardial ischemia (positive T wave), coronary angiography was normal in one patient, eight patients had single vessel, eight double vessel and four triple vessel disease. None of the patients had LM disease. The LAD was affected in 17 of the patients (81%), and of these, 15 had 90% or tighter stenosis of the vessel. Three patients had sub-total or total (diameter stenosis of 99-100%) occlusion of the LAD. The authors noted increase in the amplitude of the T wave and more

downward displacement of the ST segment as long as the ischemic event endured. The increased T-wave amplitude has been ascribed to K^+ adenosine triphosphate dependent hyperpolarization of the myocytes (Katz 2006).

6.2 Circumferential subendocardial ischemia

6.2.1 Definition

Sclarovsky introduced the concept of CSI to denote widespread ischemia of a large part of the inner layers of the LV (Sclarovsky 1999). The original definition of the term was transient ST-segment depression in the precordial leads with the maximal changes in leads V4-V5 accompanied by inverted T waves (Figures 1 and 8). Restricting the phenomenon to cases with transient changes differentiates the entity from more persistent or chronic changes typically seen in severe valve disease and LVH with remodeling (LV "strain"). On the other hand, it is not possible to know whether ST-segment depression is transient from a single ECG recording. When the ECG pattern is transient and not associated with tachycardia, it usually reflects an acute reduction in coronary blood flow. It was suggested that the changes are generally more benign during tachycardia and reflect an acute increase in myocardial demand; while in CSI, the ST-segment depressions reflect a diffuse subendocardial ischemic process.

6.2.2 Clinical study observations

In patients with widespread ST-segment depression maximally in leads V4-V6, lead aVR and III ST-segment elevation, association with triple vessel disease in coronary angiography has been demonstrated (Hasdai et al. 1995). These patients are at risk of severe heart failure, including cardiogenic shock. The potentially fatal scenario represented by a fresh occlusion of the RCA,

supplying the anterior left ventricular wall through collateral circulation to a chronically occluded LAD ("ischemia-at-a-distance") was first described in an article published during World War II (Blumgart et al. 1941).

Sclarovsky et al evaluated 46 patients with UA and maximal ECG changes confined to the precordial leads, who showed no significant changes in heart rate or blood pressure during episodes of chest pain (Sclarovsky et al. 1986a). The study showed that 26 patients developed ST-segment depression, and all of these showed changes in the leads V4 and V5, whereas 20 patients developed ST-segment elevation during the attacks. Coronary angiography showed distinct differences between the two groups. In patients with ST-segment depression, 18 had LM or LM equivalent disease (≥70% stenosis), three had double vessel and only two had single vessel disease. Three patients had normal coronary arteries. In the patients, who developed ST-segment elevation, only two had LM or its equivalent disease, four had double and 14 had single vessel disease. The authors concluded that presence of ST-segment depression in leads V4 and V5 in UA patients without evidence of increased demand may be suggestive of significant LM or LM equivalent disease. Notably, the studies in the 1980s were performed before the introduction of the more sensitive biochemical markers of myocardial injury, such as troponins. Hence, it cannot be excluded that a substantial proportion of the patients classified as UA in fact had NSTEMI.

The same investigators extended their observations by introducing the concept of the T-wave vector in NSTE-ACS patients with ST-segment depression. They noted distinct differences between patients with positive or negative T waves (Sclarovsky et al. 1988a). In 32 patients with horizontal or downward-sloping ST-segment depression confined to the precordial leads, positive T waves in the leads with ST-segment depression were found in 21 patients and negative T waves in 11 patients. None of the patients with peaked positive T waves – but seven out of 10 patients (one patient did not have angiography) with negative T waves had significant LM obstruction. It is

worthy of note that, already in the late 1980s, the authors considered patients with precordial ST-segment depression and inverted T waves to be an extremely high-risk subset of patients.

Studies in NSTE-ACS patients have shown that ST-segment depression, T-wave inversion and lead aVR ST-segment elevation are associated with higher mortality in comparison with patients without these ECG changes (Gorgels et al. 1993; Haines et al. 1983). Wide-spread ST-segment depression during anginal pain usually present in ≥6 leads, often with inverted T waves, has been linked with autopsy-proven extensive subendocardial MI without transmural involvement as well as with LM-, LM equivalent- or severe triple vessel disease (Ogawa et al. 1985). However, if the ECG was recorded when symptoms resolve, it may even be normal. In consecutive patients with angiographically proven LM disease, the most frequent ECG pattern observed during pain was ST-segment depression, especially evident in V3-V5 (maximally in lead V4) and ST-segment elevation in leads V1 and aVR. Almost identical ECG changes were present in an exercise test performed on the majority of patients, indicating similar pathophysiologic processes (Atie et al. 1991). The same group of investigators showed an association between an ECG pattern of ST-segment depression in leads I, II, and V4-V6 and ST-segment elevation in lead aVR during active chest pain, and severe CAD in angiography (Gorgels et al. 1993). In a retrospective study of 310 patients with NSTE-ACS, multivariate analysis showed that ST-segment elevation in lead aVR of ≥0.5 mm was the strongest predictor of LM or triple vessel disease, followed by positive troponin T (OR 19.7, $p<0.001$ and OR 3.08, $p=0.048$, respectively). ST-segment elevation in lead aVR of ≥0.5 mm and positive troponin T identified LM or triple vessel disease with sensitivities of 78 and 62%, specificities of 86 and 59%, positive predictive values (PPV) of 57 and 26%, and negative predictive values (NPV) of 95 and 87%, respectively ($p <0.05$) (Kosuge et al. 2005).

In 775 consecutive patients with a first NSTEMI, 437 patients were catheterized within 6 months and the ECG findings at presentation were compared with the angiographic findings (Barrabes et al. 2003). The prevalence of LM or triple vessel disease in the patients without (n=525) and with 0.5 to

1 mm (n=116) or >1 mm (n=134) of ST-segment elevation in lead aVR were 22.0, 42.6 and 66.3%, respectively (p<0.001). In another study, lead aVR ST-segment elevation (>0.5 mm) occurred with a significantly higher incidence in patients with LM obstruction (88% [n=14/16]) than in LAD (43% [n=20/46]) or RCA (8% [n=2/24]) obstruction (Yamaji et al. 2001). The amount of lead aVR ST-segment elevation was significantly higher in the LM group (1.6 +/- 1.3 mm) than in the LAD group (0.4 +/- 1.0 mm). The finding of lead aVR ST-segment elevation greater than or equal to lead V1 ST-segment elevation distinguished the LM group from the LAD group with 81% sensitivity, 80% specificity and 81% accuracy.

In a study of consecutive patients with NSTE-ACS, patients with ST-segment depression in any lead combined with ST-segment elevation in lead aVR showed severe disease in coronary angiography: 27 patients (29%) had LM and 40 patients (44%) had triple vessel disease (Taglieri et al. 2011). The LM was the culprit artery in 24 (26%) of the patients with this ECG pattern. They also found that the ECG pattern was associated with increased risk for culprit LM disease (OR 4.72, 95% CI 2.31-9.64, p<0.001), compared with patients without any ST-segment deviation – whereas patients with isolated ST-segment deviation did not.

Nasmith et al performed 99 continuous body surface potential recordings with orthogonal X, Y and Z leads in 35 patients during STEMI in 30 patients during single vessel, elective coronary angioplasty, and in 34 patients with UA or acute non-Q wave MI (De Chantal et al. 2006). It was evident that ST-segment depression vectors were confined to a small, lateral cardiac region, despite a variety of coronary lesions, while ST-segment elevation vectors were oriented according to the territory of the occluded artery (difference of direction means, p<0.002). The authors concluded that ST-segment depression in ACS is maximal over the left thorax, regardless of coronary lesion location; indicating that the mechanism of ST-segment depression is not fully understood.

Lead aVR ST-segment elevation is not specific for LM or triple vessel disease in ACS. In 100 patients with a first anterior STEMI, ST-segment elevation in lead aVR strongly predicted LAD occlusion proximal to the first septal branch (Engelen et al. 1999).

6.2.3 Autopsy study observations

Apart from animal studies, autopsy studies seem to support the hypothesis that severe CAD may induce CSI. Myers et al described 15 cases with involvement of the entire subendocardial circumference from the apex to the base of the LV (Myers et al. 1951). Premortal ECG analysis revealed that in five out of seven patients who had received no cardiac glycosides, ST-segment depression accompanied by a diphasic or inverted T wave was present.

Hackel and Wagner described an autopsy case of acute circumferential subendocardial infarction (Hackel and Wagner 1992). The patient had severe triple vessel disease and the premortal ECG showed typical ST-segment depression of subendocardial injury. Raunio et al (Raunio et al. 1979) presented 15 patients with acute subendocardial infarction at autopsy. In seven out of eight cases with circumferential MI, the premortal ECG finding was ST-segment depression. Ogawa et al (Ogawa et al. 1985) presented 93 patients with non-Q-wave MI with different types of ST-segment and T-wave changes. Forty-nine patients with ST-segment depression had a higher rate of pump failure and multivessel disease. At necropsy, five of six patients, who had shown severe ST-segment depression in many leads, were found to have large subendocardial infarctions which were circumferential or nearly circumferential in extent. Postmortem angiography in these patients showed triple vessel disease. One can assume that circumferential subendocardial infarction is preceded by a stage, where there is wide-spread (circumferential) subendocardial ischemia in the type of cases described in the autopsy materials.

6.2.4 Differential diagnosis of the ECG pattern of circumferential subendocardial ischemia

The ECG changes of CSI are not specific. They may be present as more or less constant findings in LBBB (Figure 10), pre-excitation, LVH and in patients on digitalis glycosides. The ECG pattern of ST-segment depression and negative T waves in the lateral precordial leads is seen in different clinical entities, where the end-diastolic LV pressure is increased; in spontaneous tachycardia-induced ischemia (Sclarovsky et al. 1988b), during rapid atrial pacing in patients with CAD (Grossman 1986), and in the chronic post-MI phase with restrictive LV remodeling (Assali et al. 2000).

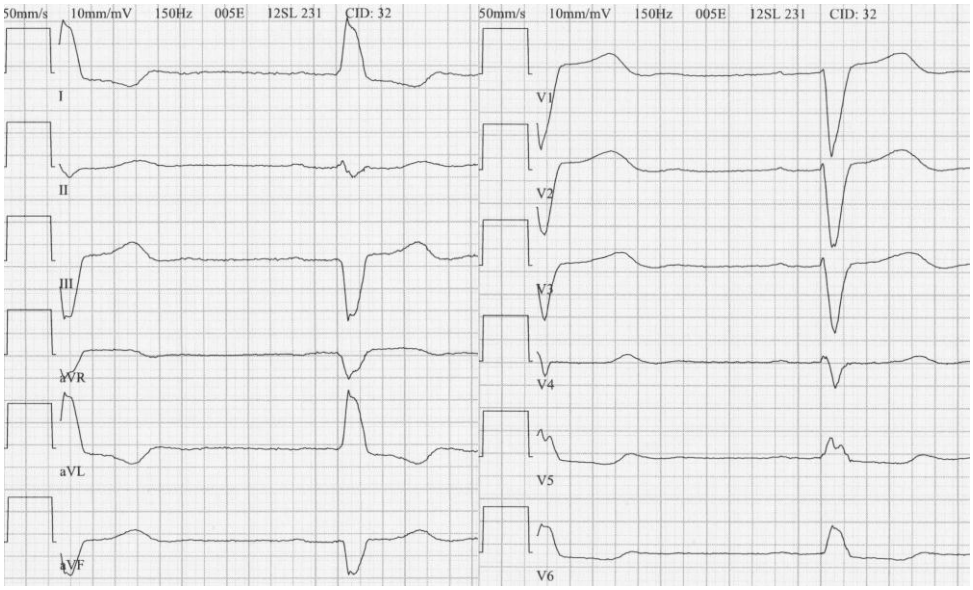

Figure 10. The 12-lead ECG shows left bundle branch block with secondary ST-segment depression in leads I, aVL, V5 and V6. There is ST-segment elevation in leads III, aVR, aVF, V1 and V2.

6.2.5 Similarities with ECG changes during the exercise test

Also, ST-segment depressions induced by an exercise test are most frequent and marked in lead V5 independently of the coronary anatomy, and they have been postulated to represent a global subendocardial phenomenon (Figure 11) (Froelicher and Myers 2000). It was also shown that

exercise test-induced ST-segment elevation in lead aVR proved to be an important indicator of significant LM or ostial LAD stenosis in stable CAD (Uthamalingam et al. 2011).

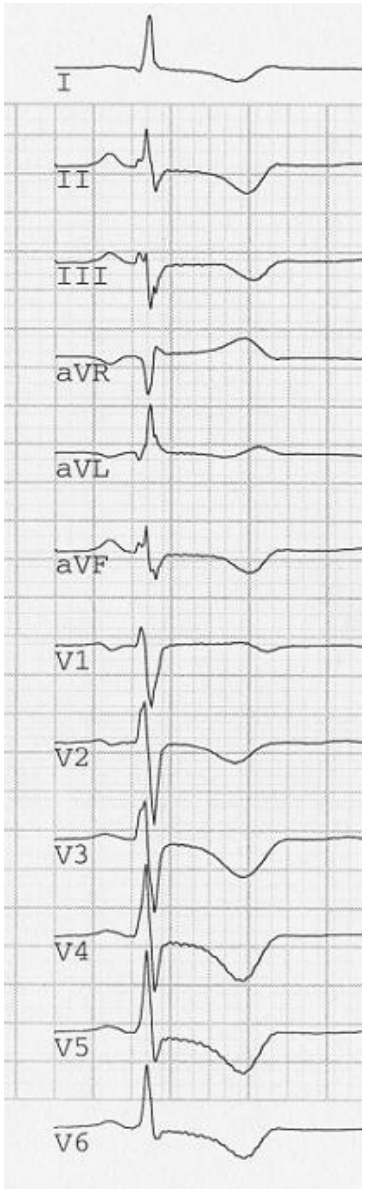

Figure 11. ST-segment changes induced by a stress test in a patient with coronary artery disease. Note that the ECG changes are identical to the ECG pattern of circumferential subendocardial ischemia: widespread ST-segment depression with inverted T waves maximally in lead V5 and ST-segment elevation in lead aVR.

Hänninen et al used body surface potential mapping in 45 patients with stable CAD and 25 healthy controls during supine bicycle exercise testing to examine ECG criteria for acute reversible

myocardial ischemia (Hänninen et al. 2001). Of the 45 patients, 18 patients had anterior, 14 had posterior, and 13 had inferior ischemia, documented by coronary angiography and thallium scintigraphy. The study results indicated that irrespective of the location of ischemia within the myocardium, the optimal location for ST-segment depression was close to leads V5 and V6. Reciprocal ST-segment elevation was found over the right shoulder, which in 12-lead ECG is represented by lead aVR.

6.3 Pre-existing changes

Up to 25% of patients presenting with NSTE-ACS will have changes confounding ECG interpretation, such as bundle branch block, LVH, the Wolff-Parkinson-White syndrome or paced rhythm (Nikus et al. 2010). There is some data indicating angiographic findings and outcome comparable to cases with major ST-segment depression for this ECG group (Owens and Adgey 2006). Also, significant benefit from an invasive therapeutic strategy has been shown. In the FRISC-II trial of NSTE-ACS, 504 patients (23%) of the study population had confounding factors on the ECG (Holmvang et al. 2003). Of these, 40 (2%) patients had LBBB, 59 (3%) RBBB, 130 (6%) left anterior hemiblock, five (0.2%) left posterior hemiblock, 175 (8%) LVH, 95 (4%) right ventricular hypertrophy, eight (0.4%) paced rhythm, two (0.09%) suspected pre-excitation and two (0.09%) low voltage. In coronary angiography, 160 patients (61.8%) had double, triple or LM disease, close to the corresponding number (68.3%) in patients with major ST-segment deviation (>5mm sum). In patients with confounding factors, mortality with the invasive and non-invasive strategy was 4.7 and 7.9%, respectively (RR 0.58, 95% CI 0.26-1.32, adjusted OR 0.48, 95% CI 0.19-1.23). For patients with major ST-segment deviations, the corresponding mortality figures were 2.7 and 4.1%. However, the numbers of patients in both groups, those with ECG confounders and those with major ST-segment deviations, were too small to obtain statistical significance.

The negative prognostic impact of LBBB has been well documented. In the Canadian ACS Registry (n=5,003), 262 patients (5.2%) had LBBB (Baslaib et al. 2010). In-hospital and one-year mortality was significantly higher in patients with LBBB compared with patients with QRS <120 milliseconds (5.0 vs 1.9%, OR 2.71, 95% CI 1.49-4.94, p=0.001, and 23.8 vs 7.7%, OR 3.74, 95% CI 2.72-5.13, p<0.001). Only LBBB was an independent predictor of one-year mortality (OR 1.93, 95% CI 1.28-2.90, p=0.002).

Confounding factors affect the ECG interpretation to a variable degree. In suspected NSTE-ACS, where there is no previous ECG recording for comparison, the diagnostic and prognostic information gained from the ECG may be suboptimal. In patients with symptoms suggestive of an ACS (n=5,324) in six U.S. hospitals, 3% had ECG-LVH, 3% had LBBB, and 3% had RBBB (Pope et al. 2004). Compared with patients without ST-segment or T-wave abnormalities, patients with ECG-LVH or bundle branch block were older and were more likely to have a chief complaint of shortness of breath or a history of cardiac or related diseases. Having ECG-LVH or bundle branch block did not alter the true-positive rate for ACS but increased the false-positive rate by almost 50%.

7. ECG in risk stratification

7.1 Prognostic value of ST-segment depression

Before the era of largely implemented invasive therapy of ACS, Sclarovsky et al retrospectively evaluated 32 patients hospitalized for UA, who developed an AMI during the same hospitalization, and who had no evidence of increased demand during episodes of chest pain (no significant changes in heart rate or blood pressure) (Sclarovsky et al. 1986b). For study inclusion, the patients had to have at least two documented attacks of chest pain with similar ECG evidence of ST-segment shifts without progressing to AMI, and the maximal ischemic ECG changes had to be confined to the

precordial leads. Eventually, UA developed into STEMI in 19 and into NSTEMI in 13. All of the STEMI patients, but none of the NSTEMI patients developed Q waves. ST-segment depression was confined to the leads V4-V6 in six patients, while seven patients had more wide-spread ST-segment depression comprising leads V2-V6. It proved that the study inclusion criteria selected a group of high-risk NSTEMI patients; nine of the 13 patients were in Killip class IV compared with one patient in the STEMI group. The remaining four patients died before they could be evaluated. Of the NSTEMI patients, ten died in hospital (77%), while one out of 19 STEMI patients died (5%) ($p<0.01$). Seven patients died in electromechanical dissociation, whereas three died in cardiogenic shock. Coronary angiography was performed in four NSTEMI patients before the development of MI. Two had 80% obstruction of the LM with additional double and triple vessel disease. The remaining two patients had LM equivalent triple vessel disease. Postmortem examination performed in four NSTEMI patients, revealed total obstruction of the LM.

7.1.1 Presence of ST-segment depression

Large trials published in the 1990s proved that the presence of ST-segment depression during an episode of ACS was a powerful and independent predictor of long-term mortality. In the ECG Ancillary Study from the TIMI Registry, which included UA and non-Q wave MI patients, the presence and degree of ST-segment and T-wave deviations were recorded (Cannon et al. 1997). New ST-segment deviation 1 mm or more was present in 14.3% of the 1,416 enrolled patients (mean age 62.5 y, >75 y 13.8%), isolated T-wave inversion in 21.9% and LBBB in 9%. By one-year follow-up, death or MI occurred in 11% of patients with 1mm or more ST-segment deviation, compared with 6.8% of patients with new, isolated T-wave inversion and 8.2% of those with no ECG changes ($p<0.001$ when comparing ST- with no ST-segment deviation). Patients with only 0.5 mm ST-segment deviation (n=187, 13%) showed a death or MI rate by one year of 16.3%, compared with 14.9, 9,7 and 6.1% in patients with ≥2 mm, ≥1 mm or no ST-segment deviation,

respectively ($p<0.001$). On multivariate analysis, ST-segment deviation of either ≥1 mm or ≥0.5 mm remained independent predictors of death or MI by one year. Among patients with ST-segment deviation ≥1 mm, changes in the anterior leads carried the worst prognosis, with a rate of death or MI of 12.4% by one year, compared with 7 to 8% for other locations or no ST-segment deviation ($p=0.002$).

Hyde et al collected consecutive patients (mean age 64 y) admitted to a coronary care unit with ischemic chest pain, but without ST-segment elevation (Hyde et al. 1999). Out of 353 patients, 173 (49%) had ≥0.5 mm ST-segment depression. At four-year follow-up, the survival rate for patients with normal ECG at baseline was 94%, while the survival rate of patients with ≥0.5 mm ST-segment depression was 82% ($p=0.02$). ST-segment depression proved to be an independent predictor of mortality (OR 1.37, 95% CI 1.20-1.55, $p=0.015$). In addition, the degree of ST-segment depression predicted outcome; of patients with ≥2 mm ST-segment depression, four year survival was only 53%, compared to 77% in those with ≥1 mm and 82% in those with ≥0.5 mm.

A retrospective ECG substudy of various ECG presentations of acute myocardial ischemia in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries- (GUSTO-) IIb study comprised a total of 12,142 patients (mean age within the sub-groups 63-67y) who reported symptoms of cardiac ischemia at rest within 12 hours of admission and had ECG signs of myocardial ischemia, either transient or persistent ST-segment elevation or depression ≥0.5 mm, or persistent and definite T-wave inversion of more than 1 mm (Savonitto et al. 1999). On the presenting ECG, 22% of the patients had isolated T-wave inversion, 28% had ST-segment elevation, 35% had ST-segment depression (alone or with concomitant T-wave inversion), and 15% had a combination of ST-segment elevation and depression. The corresponding numbers for 30-day incidence of death or MI were 5.5, 9.4, 10.5, and 12.4%, respectively ($p<0.001$). The ECG category in addition to enzyme levels of creatine kinase at admission remained highly predictive of death and MI after multivariate adjustment for the significant baseline predictors of events.

7.1.2 Sum of ST-segment depression

In another GUSTO-IIb substudy (n=5,192), multivariable logistic regression analysis showed that the sum of ST-segment depression in all leads was a powerful independent predictor of 30-day death ($p<0.0001$), with a continuous increase in risk with the extent of the ST-segment depression (Savonitto et al. 2005). The sum of ST-segment depression ($p<0.0001$), the presence of minor inferior ($p<0.0001$) or anterior ($p=0.018$) ST-segment elevation were also independent predictors of the composite of death and MI or re-infarction. The study also showed that the extent of ST-segment depression was associated with the severity of CAD. Greater amount of ST-segment depression was associated with an increased likelihood of triple vessel or LM disease. Of patients with a sum of ST-segment depression of 0-2 mm (n=2,493), 27% had triple vessel and 7.3% LM disease. The corresponding numbers for those in the highest quartile (n=1,333) with a sum of ST-depression >6 mm were 43 and 15.3%, respectively. The extent of ST-segment depression showed a highly significant correlation with the prevalence of triple vessel ($p<0.0001$) or LM disease ($p<0.0001$), and also with the peak levels of creatine kinase (<0.0001) during the index episode of ACS.

A FRISC-II substudy included 2,201 patients (Holmvang et al. 2003). The patients were classified into subgroups according to the total amount of ST-segment deviation (the summated deviation in 11 leads, excluding aVR, and the total number of leads with ST-segment deviation ≥0.5 mm) at admission. The invasive strategy produced a reduction of ~50% in death or MI among the patients with intermediate (sum of ST deviation 3-5.5 mm) and major (≥6 mm) ST-segment deviation. The findings were independent of age, gender, or troponin T status. Sums of ST-segment deviations were correlated with coronary angiography findings in 1,077 patients in the invasive arm of the study. They found that more patients with minor ST-segment deviations (sum of ST deviation 0-2.5 mm) had either non-significant or single vessel disease, whereas double or triple vessel or LM

stenosis were 50% more common among the patients with major ST depression (43.9 vs. 68.3% for sum of ST deviation 0-2.5 mm and ≥6 mm, respectively, p<0.00001).

Recently, findings by Yan et al did not support the quantification of ST-segment depression in routine clinical practice beyond simple dichotomous evaluation for the presence of ST-segment depression in NSTE-ACS (Yan et al. 2008). The study included 2,266 patients from the GRACE registry without ST-segment elevation or LBBB. Overall in-hospital and 6-month mortality numbers were 4.4 and 7.5%, respectively. When compared with patients without ST-segment depression, patients with any ST-segment depression ≥0.5 mm sustained significantly higher mortality in the hospital (5.6 vs. 2.1%, p<0.001) and at 6 months (10.5 vs. 4.7%, p<0.001). In multivariable analyses, after adjusting for all the clinical prognosticators of various GRACE risk models validated to predict in-hospital and cumulative 6-month mortality, the presence of any ST-segment depression as a dichotomous covariate remained as an independent predictor of death in hospital and at 6 months. In direct comparison with the presence of ST-segment depression, quantitative analysis for cumulative ST-segment depression provided only similar incremental risk discrimination.

7.1.3 Localization of ST-segment deviation

In a study (n=432) of consecutive patients with a first NSTEMI (Barrabes et al. 2000), the baseline ECG was normal in 54 patients (13%), minor ST-segment shifts or isolated T-wave inversion were present in 149 patients (34%), and ≥1 mm ST-segment depression in 229 (53%) of the patients. Ninety-one patients (21% of the total group and 40% of those with ST-segment depression) had lateral ST-segment depression on the admitting ECG. Leads I and aVL were involved in seven patients, leads V5 and V6 in 65, all of these four leads in 12 patients, and lead I and aVL and V5 or V6 in seven. Concomitant ST-segment depression was present in the leads V1 to V4 in 30 patients,

in the inferior leads in 10, and in the anterior plus inferior leads in 15 patients. Patients with lateral ST-segment depression were at higher risk for most in-hospital complications than patients with ST-segment depression not involving the lateral leads; pulmonary edema/cardiogenic shock was observed in 14.3 and 4.1%, respectively ($p<0.001$). Also, 30-day mortality rates were higher in the patients with than in those without lateral ST-segment depression (14.3 and 4.2%, respectively, $p=0.007$). Coronary angiography was performed in 40 patients with and 175 patients without lateral ST-segment depression. LM or triple vessel disease was present in 60% (n=24) of those with and 22% (n=39) of those without lateral ST-segment depression ($p<0.001$).

Birnbaum et al studied 1,321 patients (1,020 men) with acute inferior STEMI enrolled in the GUSTO-I trial in Israel (Birnbaum et al. 1996). They found that patients (n=113) with maximal ST-segment depression in leads V4 to V6 had the highest in-hospital mortality rate (9.7%), and in multivariable logistic regression analysis, hospital mortality was independently associated with the pattern of precordial ST-segment depression. The OR for adverse outcome in patients with maximal ST-segment depression in leads V4 to V6 relative to those with no precordial ST-segment depression was 2.78 (95% CI 1.26-6.13, $p=0.007$). The authors speculated that inferior outcome was due to multivessel CAD. Routine coronary angiography was not performed.

A recent study included 1,042 consecutive patients with NSTE-ACS, who had chest pain within 24 h plus one of the following: ST-segment deviation ≥0.5 mm in any lead, transient (<20 min) significant ST-segment elevation in 2 contiguous leads, inverted T waves ≥1 mm, positive cardiac biomarkers and documentation of CAD (Taglieri et al. 2011). Of the whole study group, 85% had NSTEMI and 15% UA. The patients were divided into 5 groups according to the ECG findings at presentation. In-hospital cardiovascular death was observed in 3.8% of the patients. On multivariable analysis, patients with ST-segment depression in any lead plus ST-segment elevation in lead aVR (n=140, 13%) showed an increased risk for in-hospital cardiovascular mortality (OR 5.58, 95% CI 2.35-13.24, $p<0.001$) compared to patients without any ST-segment deviation,

whereas patients with isolated ST-segment deviation did not. At one-year follow-up, 127 patients (12.2%) died from cardiovascular causes. On multivariable analysis, ST-segment depression plus ST-segment elevation in lead aVR was a stronger independent predictor of cardiovascular death (HR 2.29, 95% CI 1.44-3.64, p<0.001) than isolated ST-segment deviation (HR 1.52, 95% CI 0.98-2.36, p=0.06).

In the study of Barrabes et al of 775 consecutive patients with a first NSTEMI, the rates of in-hospital death in patients without (n=525) and with 0.5 to 1 mm (n=116) or >1 mm (n=134) of ST-segment elevation in lead aVR were 1.3, 8.6, and 19.4%, respectively (p<0.001) (Barrabes et al. 2003). After adjustment for the baseline clinical predictors and for ST-segment depression on admission, the OR for death in the last 2 groups were 4.2 (95% CI, 1.5-12.2) and 6.6 (95% CI, 2.5-17.6), respectively. The rates of recurrent ischemic events and heart failure during the hospital stay also increased in a stepwise fashion among the groups, whereas creatine kinase-MB levels were similar.

7.2 Prognostic value of the T wave

The potential prognostic value of the ECG in patients with NSTE-ACS was appreciated in the early 1980s. In general, ST-segment depression was considered a stronger marker of inferior outcome than T-wave inversion. However, a subgroup of patients with adverse outcome was described by de Zwaan et al (de Zwaan et al. 1982). The authors studied 145 consecutive patients admitted due to UA. Of these, 26 patients (18%) showed a typical pattern of the ST-T segment in leads V2-V3, consisting of an isoelectric or minimally (1 mm) elevated takeoff of the ST segment from the QRS complex passing into a symmetrically inverted T wave. Twelve of 16 patients (75%) who did not have CABG developed a usually extensive anterior wall infarction within a few weeks after admission.

7.2.1 Isolated T-wave inversion

Haines et al studied 118 consecutive patients with the diagnosis of UA in the early 1980s with special emphasis on T-wave analysis (Haines et al. 1983). Overall, new T-wave inversions ≥2 mm occurred in 47 (40%) of the patients. The 71 patients treated medically were followed 16 ±9 months for clinical events. Of 26 patients who had T-wave inversion, 10 (38%) had either AMI or death, compared with seven (16%) of the patients without T-wave inversion ($p<0.05$). Of the 10 patients with T-wave inversion, who had a cardiac event, six had anterior T-wave inversion.

In a GUSTO-IIb study, the patients who had isolated T-wave inversion had a 6-month mortality of 3.4% (95% CI 2.8-4.2) compared to 6.8% (95% CI 6.0-7.8) of those with ST-segment depression (Savonitto S JAMA 1999). After adjusting for factors associated with an increased risk of 30-day death or re-infarction, compared with those with T-wave inversion only, the OR was 1.62 (95% CI 1.32-1.98) in those with ST-segment depression.

In the study by Hyde et al, of patients with ischemic chest pain, but without ST-segment elevation, 57 (16%) had isolated T-wave inversion (Hyde et al. 1999). At 4-year follow-up, the survival rate for these patients was 84% ($p=0.057$ compared with normal ECG), which was intermediate between the survival rate for patients with normal ECG at baseline (94%) and for patients with ≥0.5 mm ST-segment depression (82%). T-wave inversion was not an independent predictor of mortality.

The Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study compared low-molecular weight heparin with unfractionated heparin in NSTE-ACS. In an ECG substudy, out of 3,033 patients, 514 (17%) had T-wave inversion, 747 (25%) ST-segment depression, and 640 (21%) had ST-segment elevation (Goodman et al. 2006). With respect to outcome, patients with isolated T-wave inversion behaved similarly to those without ST-T changes. Death or MI at one year was observed in 45 patients (8.8%) with inverted T waves, compared to 77 patients (12%) with ST-

segment elevation, 151 patients (20.2%) with ST-segment depression, and 92 patients (8.1%) with other ECG findings (including normal ECG).

Lin et al studied 5,582 patients, 70% of whom were African American, with a potential ACS without ST-segment elevation or depression (Lin et al. 2008). During the initial hospital stay, 190 patients had cardiac catheterization, 84 patients had PCI and 14 CABG, while 698 received a stress test. Of these patients, 4,166 (75%) had no T-wave abnormalities, while 25% had different types of T-wave abnormalities. The composite endpoint of death, MI, PCI or CABG, and signs of CAD on an exercise test, was more common in patients with T-wave flattening (8.2 vs. 5.7%, RR=1.4, 95% CI 1.1-1.9, p=0.0001), T-wave inversion 1-5 mm (13.2 vs. 5.7%, RR 2.4, 95% CI 1.8-3.1 p=0.0001) and T-wave inversion >5 mm (19.4 vs. 5.7%, RR 3.4, 95% CI 1.7-6.1, p=0.0001) or any T-wave abnormality (10.8 vs. 5.7%, RR 1.9, 95% CI 1.6-2.3, p=0.0001), respectively, compared with patients without T-wave abnormalities, even after adjustment for initial troponin levels.

In the FRISC-II ECG substudy, inverted T waves were considered present if the T wave was isoelectric, negative, or biphasic in leads V2-V6, aVL (if R >5 mm), I and II (Diderholm et al. 2002). At least 1 mm T-wave inversion was required in leads V2 and aVF. In V1, aVR, and III T waves were not evaluated. Isolated T-wave inversion was found in 871 patients (36%). Within 12 months, in the invasive group, revascularization was needed in 72% compared to 85% in those with ST-segment depression ($p<0.05$). In the patients randomized to the non-invasive group, the corresponding numbers were 39 and 51%, respectively ($p<0.05$). In the whole study group, the risk of death or MI at 12 months in patients with T-wave inversion was 10.5%, which was similar to the risk for patients with no ST/T changes.

7.3 Prognostic value of regional subendocardial ischemia

In a series of consecutive patients with rest angina without tachycardia, 21 out of 32 patients showed horizontal or downward-sloping ST-segment depression accompanied by positive T waves

(Sclarovsky et al. 1988a). No patients with positive T waves (regional subendocardial ischemia) died in hospital, while three patients with inverted T waves died (p=0.03). Re-ischemia and re-infarction was observed in seven of the 21 patients; no statistically significant differences between the groups were observed for these endpoints.

One-year mortality was retrospectively correlated with location of ST-segment depression (leads I and aVL; II, III and aVF; V1-V3; or V4-V6) and T-wave polarity in 6,770 patients with NSTE-ACS randomly assigned in the GUSTO-IIb trial (Atar et al. 2007). In none of the four lead groups studied did ST-segment depression and positive T wave prove to be independently associated with one-year mortality.

7.4 Prognostic value of circumferential subendocardial ischemia

In the small study by Sclarovsky et al, 11 out of 32 NSTE-ACS patients with rest angina showed horizontal or downward-sloping ST-segment depression accompanied by inverted T waves confined to the precordial leads (Sclarovsky et al. 1988a). Despite similar baseline demographic data and proportion of MI, in-hospital outcome was inferior compared to that of patients with ST-segment depression and positive T waves. Of the 11 patients with inverted T waves (CSI), three died in hospital, compared to no deaths in the group where the T wave was positive (p=0.03), while re-ischemia and re-infarction was observed in five out of 11 and seven out of 21 patients, respectively (p=non-significant).

In the previously mentioned GUSTO-IIb study, ST-segment depression in any of the four pre-specified ECG locations was associated with higher mortality compared with patients without ST-segment depression (Atar et al. 2007). Patients with ST-segment depression and T-wave inversion in leads V4 to V6 had the highest one-year mortality rate of all groups (16.2%), and significantly higher compared with patients with ST-segment depression without T-wave inversion in those leads

(16.2 and 9.0%, respectively, p=0.001). In logistic regression analysis, sum of ST-segment depression (OR 1.061, 95% CI 1.035-1.087, p<0.001), and ST-segment depression with T-wave inversion in leads V4 to V6 (OR 1.374, 95% CI 1.023-1.844, p=0.035) were independent predictors of one-year mortality. Conversely, ST-segment depression without T-wave inversion in leads V4 to V6 or other ECG presentations were not independent predictors of one-year mortality.

AIMS OF THE STUDY

The aims of the present study were:

1. to investigate the significance of ST-segment depression and T-wave changes in ACS, with respect to in-hospital prognosis, troponin levels and angiographic findings (**I**);

2. to evaluate the prognostic significance of the three different clinical entities of ACS in prospectively collected consecutive patients from a university hospital (**II**);

3. to study the distribution of various ECG patterns on admission in patients with ACS and to define the prognostic value of these pre-defined patterns: in particular, the impact of the CSI ECG pattern on outcomes (**III**);

4. to compare preoperative 12-lead ECG findings during anginal pain in patients with and without LM disease who underwent isolated urgent or emergent bypass surgery and, specifically, to study the sensitivity, specificity and predictive values for the CSI ECG pattern recorded during anginal symptoms before isolated urgent or emergent CABG to predict angiographic LM disease (**IV**).

MATERIALS

1. Patients

The study populations for all four studies were collected at Tampere University Hospital, Finland.

1.1 Study I

From November 2000 to March 2002, patients in Tampere University Hospital with ACS and transient ECG changes were collected prospectively and consecutively. Inclusion criteria were symptoms of myocardial ischemia associated with 1) ST-segment depression (irrespective of orientation of the T wave) or T-wave inversion, in a 12-lead ECG recorded during anginal pain, 2) a positive troponin test, and 3) coronary angiography performed during the hospital stay.

Exclusion criteria were ST-segment elevation (apart from leads aVR or V1), heart rate >100 beats/min during the ECG recording, structural heart disease or previous CABG. Patients with chronic ECG changes – pathological Q waves, LVH, bundle branch block, pre-excitation or pacemakers – were also excluded.

1.2 Studies II and III

The TACOS (Tampere Acute COronary Syndrome) study enrollment region encompassed the city of Tampere and 11 neighboring municipalities, a total of 340,000 inhabitants. In this region, practically all patients with ACS were admitted to Tampere University Hospital. Patients were collected by a study nurse and two of the investigators. During a study period from 1 January 2002 to 31 March 2003, all patients admitted to the emergency department of the hospital presenting with

AMI as verified by elevated blood troponin (cTnI >0.2 μg/L) value were recruited. In addition, all consecutive troponin-negative patients with UA from 1 September 2002 to 31 March 2003 were recruited. Patients initially treated for ACS in other hospitals or those transferred from another department within the university hospital were not included. Patients who died in or were discharged from the emergency department were not included. The final study population, from which all statistical analyses were performed, consisted of 1,188 patients, 343 (29%) with STEMI, 655 (55%) with NSTEMI and 190 (16%) with UA. The patients were categorized according to the definitions described previously. During the study period when all three ACS categories were included – 1 September 2002 to 31 March 2003 – the following relative proportion of patients (n=588) was observed: 143 (25%) with STEMI, 255 (43%) with NSTEMI and 190 (32%) with UA.

1.3 Study IV

The original study population consisted of 1,131 patients, who had isolated CABG in Tampere University Hospital between May 1999 and November 2000. Of the procedures, 400 (35.4%) were performed urgently and 42 (3.7%) as emergencies. For the present study, the criteria for inclusion were the existence of a preoperative 12-lead ECG recorded during anginal symptoms, significant LM stenosis in coronary angiography and urgent or emergent CABG performed during the hospital stay. Patient files and ECGs from 132 patients, who underwent urgent or emergent CABG, and who had significant LM stenosis, were analyzed (LM+ group). For the control group, we randomly chose 132 patients, who also underwent urgent or emergent CABG, but who had no significant LM stenosis on angiography (LM- group). A total of 80/132 (61%) patients from the LM+ group and 65/132 (49%) patients from the LM- group were included in the final study group. The reasons for patient exclusion in the LM+ group were: no ECG during pain (n=31), LVH (n=4), Q waves or QRS duration >120 ms, including LBBB and RBBB and non-specific intra-ventricular block

(n=18), redo-operation (n=4). In the LM- group, patient exclusion was due to: no ECG during pain (n=53), LVH (n=2), Q waves or QRS duration >120 ms (n=11), and pacemaker ECG (n=2).

2. Ethical aspects

The Ethics Committee of Tampere University Hospital accepted the study protocols and written consent was obtained from all study participants.

METHODS

1. ECG analysis

1.1 Study I

A standard 12-lead ECG with maximal ST-segment depression was chosen for measurements. The ECG was recorded at a paper speed of 50 mm/sec at a calibration of 1 mV = 10 mm. Three investigators blinded to the angiographic findings analyzed the ECGs manually. If the results were not in accordance, consensus was found by discussion between the investigators. ST-segment deviation from the isoelectric line, determined by drawing a line between subsequent PQ segments, was considered elevated or depressed if it was 0.5 mm or more above or below the isoelectric line, respectively. The ST segment was measured 0.06 s after the J point. The T wave was considered positive or negative if it was 1 mm or more above or below the isoelectric line, measured more than 120 ms after the J point. The ST-segment and T-wave changes were measured separately from all 12 leads with the aid of a handheld magnifying lens. LVH was defined by Sokolow-Lyon criteria (SV1+RV5-6 ≥35 mm) (Sokolow and Lyon 1949). Pathological Q waves were defined as follows: 1) in leads V1-V3 any Q wave ≥30 msec in duration, 2) in leads I, II, aVL, aVF, V4-V6 Q wave ≥1 mm in height and ≥30 msec in duration in ≥2 adjacent leads and 3) in leads V1-V2, R-wave duration >40 msec and R/S ratio >1 in the absence of pre-excitation, right ventricular hypertrophy or RBBB (Cannon et al. 2001b; Perloff 1964).

Based on the ECG findings, the patients were divided into two groups: 1) patients with ST-segment depression and a *negative* T wave maximally in leads V4-V5 (T- group), and 2) patients with ST-segment depression and a *positive* T wave in the precordial lead, with maximal ST-segment depression (T+ group).

1.2 Study II

An ECG recorded in the emergency department, in the ambulance or at the referring health center showing the maximal ischemic changes was chosen for analysis. Two of the investigators analyzed the ECGs manually with the aid of a handheld magnifying lens. If the results were not in accordance, consensus was found by discussion between the investigators. ST-segment deviation and pathological Q waves were defined as in Study **I.**

1.3 Study III

We analyzed the patient ECG recorded either pre-hospitally or in the emergency department showing maximal ischemic changes. If the ECG in the referral unit was normal but a follow-up ECG in the emergency department showed ST-segment deviation, the second one was used for analysis. No ECGs recorded during hospital stay – for example, in the coronary care unit or in the catheterization laboratory – were used. All the ECGs were analyzed by two investigators blinded to the clinical data with the aid of a hand-held magnifying lens. ST-segment deviations and T-wave changes were defined as in Studies **I** and **II**.

1.3.1 Classification of ECG categories

The patients were classified into seven different ECG categories: 1) ST-segment elevation (elevation of the ST segment ≥2 mm in two contiguous precordial leads or ≥1 mm in two contiguous limb leads), 2) pathological Q waves without ST-segment elevation (Q-wave definition as in Study **I**), 3) typical LBBB (Willems et al. 1985), 4) LVH without ST-segment elevation, except in leads aVR and/or V1 (LVH was defined in accordance with the Sokolow-Lyon criteria and/or the Cornell voltage-duration product (Norman and Levy 1995), 5) CSI ECG pattern, 6) other ST-segment depression and/or T-wave inversion, and 7) other findings, including normal ECG. The

classification into the ECG categories was based solely on the actual qualifying ECG. No comparison to previous ECGs was done.

1.4 Study IV

All in-hospital and, if applicable, pre-hospital ECGs recorded within six months before CABG of both patient groups were traced. If recorded outside our hospital, the ECGs were requested and sent to the investigators. ECGs were received from 15 hospitals, 15 health centres and one private medical practice.

ECGs were classified for analysis if there was a mark confirming symptoms during the recording or if exact timing of recording during pain was clearly stated in the medical records. In case of more than one ECG recorded during pain, the one with maximal ischemic changes was chosen for analysis.

All the ECGs were analyzed manually with the aid of a handheld magnifying lens. RBBB and LBBB were defined by standard criteria (Willems et al. 1985). Non-specific intra-ventricular conduction block was defined as QRS-duration >120 ms in the absence of typical bundle branch block or pacemaker ECG. LVH was defined according to the Sokolow-Lyon criteria. The ECG diagnosis of CSI was based solely on the actual qualifying ECG. No comparison with previous ECGs was done. ST-segment and T-wave changes were defined as in Studies **I-III.**

1.5 Regional subendocardial ischemia

The definition of regional subendocardial ischemia in patients with suspicion of ACS was: ST-segment depression ≥0.5 mm and a positive T wave ≥1 mm in ≥2 parallel leads measured more than 120 ms after the J point in the precordial lead with maximal ST-segment depression (Figure 9). To qualify for the ECG pattern, ST-segment elevation (apart from leads aVR or V_1), heart rate >100

beats/min, pathological Q waves, LVH, RBBB or LBBB, pre-excitation or pacemaker ECG are not allowed.

1.6 Circumferential subendocardial ischemia

The definition of CSI was as follows, ST-segment depression ≥0.5 mm in ≥6 leads, maximally in leads V4-V5 with inverted T waves ≥1 mm more than 120 ms after the J point and ST-segment elevation ≥0.5 mm in lead aVR (Figure 1). To qualify for the ECG pattern, LVH, pathological Q waves or QRS duration >120 ms, including LBBB or RBBB or non-specific intra-ventricular block, pre-excitation or pacemaker are not allowed.

2. Echocardiography

In studies **II** and **III**, transthoracic echocardiography was performed according the hospital practice. In all patients, who had coronary angiography, the examination was performed. In patients without invasive evaluation, echocardiography was not performed routinely. Hence, out of 1,188 patients, echocardiography data was available in 557 patients. The clinicians who performed the studies decided what methods to use for ejection fraction measurements.

3. Coronary angiography

Selective coronary angiography with multiple projections was performed and the indication for angiography was clinical, not investigational, in all four studies. A significant stenosis was defined as >50% diameter obstruction of the coronary artery lumen diameter. The interpreters of the angiography were blinded to the ECG findings. In Study **I,** LM equivalent disease was defined as a diameter stenosis of >50% in the proximal segments of the LAD and LCx. Severe triple vessel

disease was defined as significant or total obstruction of the proximal or mid-segment of all three main epicardial coronary arteries. Other cases with triple vessel disease were classified as non-severe. Flow in the coronary arteries was graded into four grades (0-3), as described in the TIMI trial (Chesebro et al. 1987). Briefly, TIMI 0 represents no antegrade flow distal to the obstruction; TIMI 1 flow represents flow distal to the occlusion, but the entire coronary bed distal to the occlusion is not opacified. TIMI flow grade 2 represents slow filling and TIMI flow grade 3 normal filling of the distal coronary bed. Collateral circulation was classed into four grades in accordance with the grading system of Rentrop et al. (Rentrop et al. 1985). Briefly, grade 0 was no collateral opacification, grade 1 filling of side branches, grade 2 partial and grade 3 complete filling of the main branch by collateral vessels.

4. Classification of acute coronary syndrome categories (II)

The ACS categories were defined according to the presenting ECGs and biomarkers of myocardial necrosis. The type of MI was categorized based on the presenting ECGs. STEMI was predefined as ST-segment elevation in ≥2 adjacent leads: in leads V1-V6 ≥1.5 mm (≥2 mm in ≥1 lead); in leads II, III, aVF, I and aVL ≥1 mm and elevated biomarkers. The remaining patients with elevated cTnI levels, also those with LBBB, were categorized as having NSTEMI. UA patients showed no elevation in a minimum of 2 cTnI levels 6-12 hours apart; the ECG changes were not predefined.

5. Statistical methods

Categorical variables were expressed as numbers of patients or percentages and continuous variables as means or medians followed by inter-quartile range (IQR). We used the chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney test for numerical variables. A

two-tailed p-value of <0.05 was considered statistically significant. CIs were calculated at the 95% significance level.

The sensitivity, specificity, positive and negative predictive values of the CSI pattern to predict severe triple vessel, LM or LM equivalent disease in coronary angiography was calculated (**I**).

The Kaplan-Meier product-limit method was used to estimate 28-days unadjusted survival in study **II** and composite end-point rates in study **III.** Comparison of 28-day survival rates between three ACS categories (**II**) and rates between the CSI and other ECG patterns (III) were performed using the log-rank test.

In Studies **II, III and IV,** the Cox proportional model was used to obtain HRs. In study **II**, adjustment for baseline and in-hospital variables was done.

Variables with p<0.20 in the Cox univariate analysis, excluding variables with missing data for a significant proportion of patients, were included in the multivariate model. A stepwise backward elimination method was used to perform variable selection, each time excluding the one variable with the highest p-value. Variables with a p<0.05 were included in the final model. Age and gender adjustment was included (**III).**

In study **IV,** age, gender, history of stroke, diabetes, hypertension and smoking were included in the multivariate model. All calculations were performed with the SPSS statistical package.

RESULTS

1. Baseline demographics and distribution of acute coronary syndrome categories

1.1 Baseline data in all-comers

In Studies **II** and **III**, the study population consisted of 1,188 patients, 343 with STEMI, 655 with NSTEMI and 190 with UA. The median age of the whole study cohort was 71 (63–80), of women 75 (70–82) and men 66 (59–76). Patients with NSTEMI were older, more often female, hypertensive, had type II diabetes more often, and had higher serum creatinine levels than patients in the STEMI and UA groups. Troponin level at arrival and 6–12 h later was higher in STEMI than NSTEMI patients. STEMI patients were more often active smokers, but were less often on aspirin, beta-adrenergic receptor blocker, calcium antagonist, nitrate, digitalis, diuretic, angiotensin converting enzyme inhibitor or warfarin medication than the other groups. C-reactive protein levels at arrival differed significantly between the groups, being higher in the NSTEMI and UA group than in the STEMI group ($p<0.001$). UA patients had higher systolic blood pressure, were relatively more often non- or ex-smokers and more often on aspirin, beta-adrenergic receptor blocker, nitrate or statin medication than the AMI patients.

1.2 Distribution of ECG changes in all-comers

Figure 12 illustrates the distribution of the seven ECG categories (**III).** ST-segment elevation proved to be the most frequent (29%), followed by old Q-waves without ST-segment elevation (23%). A significant proportion of patients (13%) had a normal 12-lead ECG. The CSI ECG pattern

was present in 97 (8%) patients. Patients with the CSI ECG pattern, LBBB and LVH were older than those from the four other categories, while patients with the CSI ECG pattern more often had hypertension, diabetes, prior angina, and severe anginal symptoms. They were also more often on aspirin, beta-adrenergic receptor blocker, nitrate and diuretic medication. Systolic dysfunction based on echocardiographic ejection fraction measurement was more often seen in patients with LBBB and old Q waves. Patients with other ST-segment depression and/or T-wave inversion had the lowest troponin levels.

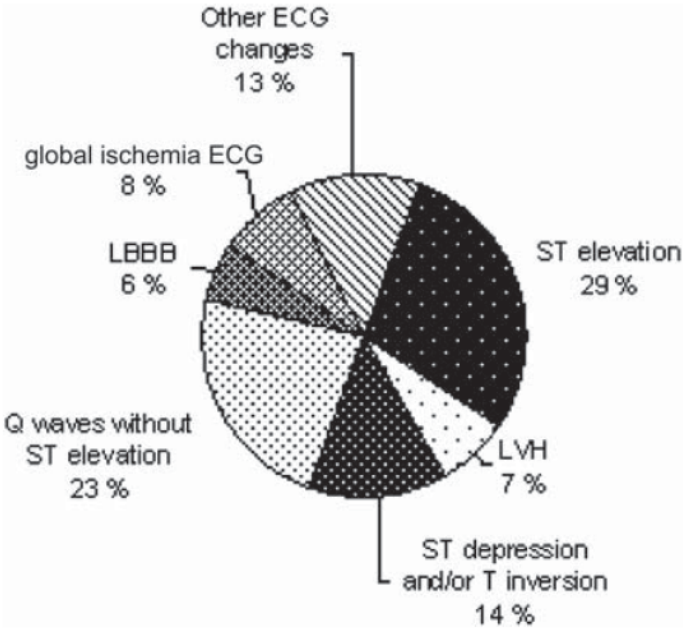

Figure 12. Distribution of ECG changes of all consecutive patients admitted with acute coronary syndrome. Rates are based on the TACOS study, n=1,188.

1.3 Baseline data in coronary artery bypass grafting patients (IV)

In the LM+ and LM- patient groups, the age distribution was 70 (62-75) and 67 (59-73) (p=0.17), and the proportion of male patients 58 and 65% (p=0.40), respectively. Also regarding risk factors for CAD and medication, the two groups were similar.

1.4 Acute coronary syndrome categories in patients undergoing urgent or emergent bypass grafting (IV)

In the LM+ group, 28 (35%) patients had UA, 43 (54%) NSTEMI and 7 (9%) patients had STEMI. Two patients did not have ACS. In the LM- group the corresponding numbers were 27 (42%), 27 (42%) and 11 (17%) patients, respectively. In the patients with MI, a final diagnosis of Q-wave MI was established in 6 and 8 patients in the LM+ and LM- groups, respectively. No significant differences between the two groups were found with respect to baseline characteristics.

2. Correlation of the ECG pattern of circumferential subendocardial ischemia with angiographic findings

The culprit artery could be defined in only three of 25 cases in the patients in the T- group (**I**). One patient had an acute plaque rupture of the LM. In two cases, there was significant stenosis in the LM without any other significant stenoses. In the patients in the T+ group, the culprit artery could be defined in 76% of cases (LAD in 74, LCx in 26%). Rentrop collateral flow Grade 0 or 1 on angiography was present in 68% in the T- group and in 92% in the T+ group, and Grade 2 or 3 in 32 and 8% respectively ($p = 0.07$). All patients in the T- group had severe triple vessel, LM or LM equivalent disease. All patients with severe triple vessel disease presented with the CSI ECG pattern.

The pre-specified ECG pattern consisting of ST-segment depression and a negative T wave maximally in leads V4-V5 (CSI ECG pattern) had a sensitivity of 93% and a specificity of 100% to predict LM, LM equivalent or severe triple vessel disease in coronary angiography. Also the PPVs and NPVs were high, 100 and 92%, respectively. Regarding invasive therapy, the majority of the

patients in the T- group needed CABG, compared to only 20% of the patients in the T+ group ($p<0.001$).

In Study **III,** coronary angiography during the hospital stay was performed on 560 patients (47%). Of these, 71% of the patients with the CSI ECG pattern had triple vessel disease in coronary angiography. LM disease either isolated or in association with single, double or triple vessel disease was present in 25% of the patients. The corresponding numbers for other ST-segment depression and/or T-wave inversion was only 22% for triple disease and 3% for LM disease. Also, revascularization during hospital stay was more frequent in patients with the CSI ECG pattern than in patients from the other ECG categories.

In Study **IV,** seven patients (11%) in the LM- group had single, 11 patients (17%) double, and 47 patients (72%) triple vessel disease. The CSI ECG pattern during anginal pain was found in 61 of 80 patients (76%) with LM disease and in 12 of 65 patients (19%) without LM disease. The most frequent (43%) ECG presentation in the LM- patients was ST-segment depression with positive T waves.

The pre-specified CSI ECG pattern had a sensitivity of 76% and a specificity of 81% to predict significant LM stenosis on angiography. Also, the PPVs and NPVs were high – 84 and 74%, respectively.

3. Outcome in acute coronary syndrome

3.1 According to acute coronary syndrome categories

Unadjusted in-hospital crude mortality in the whole study cohort of 1,188 patients was 10.4% (**II**). Mortality increased to 23% during a median follow-up time of 10 months. In-hospital mortality for

the STEMI, NSTEMI and UA categories was 9.6 (n=33), 13 (n=85), and 2.6% (n=5), respectively (p<0.001). The corresponding numbers for the whole follow-up period were 19 (n=66), 27 (n=179), and 12% (n=22), respectively (p<0.001). In univariate Cox regression analyses, the STEMI category compared with the UA category predicted mortality at follow-up with a HR of 3.41 (95% CI 2.04-5.69, p<0.001). The corresponding number for the NSTEMI category was 5.74 (95% CI 3.54-9.29, p<0.001). In the final multivariate Cox regression model, the STEMI category compared to the UA category predicted mortality with a HR of 3.47 (95% CI 2.06-5.86, p<0.001). The corresponding HR for the NSTEMI category was 3.89 (95% CI 2.39-6.32, p<0.001).

3.1.1 Predictors of mortality

We confirmed the prognostic importance of several baseline characteristics with respect to mortality at follow-up (Table 1) (**II**). The prognostic significance of the variables retained in the final multivariate Cox regression model is presented in Table 2.

Table 1. Prognostic significance of selected variables concerning mortality at follow-up in acute coronary syndrome (median 10 months) according to univariate Cox regression analyses

Variable	Median (IQR) Or%	Valid cases	p-value	Hazard ratio	95% CI
Age	73 (63-80)	1188	<0.001	1.07	1.058-1.086
Female gender	42	1188	0.002	1.458	1.147-1.855
Diabetes					
No diabetes	74	1184		1	
Diabetes mellitus type 1	1	1184	0.233	1.828	0.678-4.928
Diabetes mellitus type 2	25	1184	<0.001	1.720	1.332-2.221
Previous MI	24	1172	0.014	1.388	1.068-1.804
Creatinine at admission (µmol/l)	85 (71-106)	1187	<0.001	1.005	1.004-1.006
CRP at admission (mg/l)	4.1 (1.5-16)	1170	<0.001	1.005	1.003-1.007
Systolic blood pressure	145 (126-166)	1187	<0.001	0.988	0.984-0.993
Diastolic blood pressure	80 (69-91)	1187	<0.001	0.984	0.977-0.991
Medication at admission					
Diuretic	34	1186	<0.001	2.798	2.194-3.567
Statin	22	1187	<0.001	0.511	0.363-0.718
ACE-inhibitor	22	1185	0.026	1.361	1.038-1.785
PCI	15	1188	<0.001	0.424	0.266-0.677
CABG	9	1188	0.016	0.490	0.275-0.875
Category of ACS		1188			
UA	16			1	
STEMI	29		<0.001	3.405	2.038-5.688
NSTEMI	55		<0.001	5.736	3.542-9.289
CAG data available		470			
<50% stenosis	11			1	
1-vessel disease	31		0.835	1.182	0.245-5.704
2-vessel disease	27		0.403	1.924	0.415-8.916
3-vessel disease	32		0.030	4.938	1.168-20.878
Left main disease*	8	470	<0.001	3.560	1.749-7.246

IQR=inter-quartile range, MI= myocardial infarction; CRP=C-reactive protein; ACE=angiotensin converting enzyme inhibitor; PCI=percutaneous coronary intervention during hospital stay; CABG=coronary artery bypass surgery during hospital stay; ACS=acute coronary syndrome; STEMI=ST-elevation myocardial infarction; NSTEMI=non-ST elevation myocardial infarction; UA=unstable angina pectoris. CAG=coronary angiography; *Either isolated or in association with 1-, 2- or 3-vessel disease

Table 2. Variables retained in the final multivariate Cox regression model regarding mortality at follow-up (median 10 months) in patients with acute coronary syndrome.

Variable	Hazard ratio	95% CI	p-value
Age years	1.049	1.034-1.064	<0.001
Diabetes			
No diabetes	1		
Diabetes mellitus type 1	3.738	1.344-10.394	0.012
Diabetes mellitus type 2	1.180	0.904-1.540	0.225
Diuretic use on admission	1.389	1.052-1.833	<0.001
Serum creatinine	1.003	1.002-1.005	<0.001
Systolic blood pressure	0.992	0.988-0.996	<0.001
Category of ACS			
UA	1		
STEMI	3.473	2.060-5.855	<0.001
NSTEMI	3.883	2.387-6.318	<0.001
PCI	0.595	0.355-1.000	0.050
CABG	0.562	0.304-1.041	0.067

ACS=acute coronary syndrome; STEMI=ST-elevation myocardial infarction; NSTEMI=non-ST elevation myocardial infarction; UA=unstable angina pectoris; PCI=percutaneous coronary intervention during hospital stay; CABG=coronary artery bypass grafting during hospital stay

3.2 According to ECG patterns

3.2.1 All-comers

The outcome of seven prespecified ECG patterns was evaluated (**III**). Table 3 illustrates the patient outcome according to ECG category in the unadjusted univariate analysis. In-hospital mortality rate was highest among patients with LBBB and the CSI ECG pattern. The incidence of in-hospital composite endpoints was lowest in patients with LVH, ST-segment elevation and other ST-segment depression and/or T-inversion.

Table 3. In-hospital outcome by ECG categories in patients with acute coronary syndrome, n=1,188.

ECG category	STE	STD and/or T-inv	CSI-ECG	LBBB	LVH	Q wave	Other ECG changes	p-value
	n=349 n (%)	n=160 n (%)	n=97 n (%)	n=71 n (%)	n=82 n (%)	n=272 n (%)	n=157 n (%)	
Composite endpoints[a]	54 (16)	22 (14)	28 (30)	15 (21)	10 (12)	58 (21)	36 (23)	0.009
Death	23 (7)	13 (8)	14 (14)	13 (18)	4 (5)	34 (13)	22 (14)	0.004

[a] death, resuscitation, re-infarction, unstable angina or stroke; ECG=electrocardiogram; STE=ST-segment elevation; STD=ST-segment depression; T-inv=T-inversion; CSI=cirumferential subendocardial ischemia; LBBB=left bundle branch block; LVH=left ventricular hypertrophy

The CSI ECG pattern predicted a high rate of composite endpoints (48%) at 10 months follow-up compared to all the other ECG categories (36%) (HR 1.78, 95% CI 1.31-2.41, p<0.001). In multivariate analysis, the CSI ECG pattern, age, creatinine level at presentation and diabetes were identified as independent predictors for poor prognosis at 10-month follow-up (Table 4).

Table 4. Variables retained in the final multivariate Cox proportional model examining the rate of composite endpoints at 10-month follow-up.

Variable	Hazard ratio	95% CI	p-value
Age	1.04	1.03-1.05	<0.001
Gender	1.10	0.90-1.36	0.363
Systolic blood pressure	0.97	0.94-1.00	0.053
Plasma creatinine	1.003	1.002-1.004	<0.001
Diabetes	1.48	1.07-2.05	0.017
No diabetes	1		
Diabetes mellitus type I	2.65	1.16-6.07	0.021
Diabetes mellitus type II	1.12	0.91-1.39	0.227
Diuretic use on admission	1.24	0.998-1.54	0.052
Circumferential subendocardial ischemia ECG pattern	1.40	1.02-1.91	0.035

CI=confidence interval; ECG= electrocardiogram

3.2.2 Regional and circumferential subendocardial ischemia

We compared in-hospital outcomes between regional subendocardial ischemia and CSI (**I**). Table 5 illustrates the marked differences between the two groups concerning rate of heart failure, LV function and outome. One out of four patients presenting with the CSI ECG pattern died in hospital, despite a high rate of invasive therapy.

Table 5. In-hospital follow-up

Variable	**CSI**	**Regional ischemia**	**p-value**
	n=25	n=25	
	%	%	
Clinical signs of heart failure	40	4	0.005
Ejection fraction			
30-49%	42	8	0.008
≥ 50%	58	92	0.008
CABG	76	20	<0.001
PCI	12	52	0.005
In-hospital mortality	24	0	0.02

CSI=circumferential subendocardial ischemia; CABG=coronary artery bypass grafting; PCI=percutaneous coronary intervention

DISCUSSION

1. General considerations

The present study established the clinical importance of the ECG pattern of CSI to predict severe CAD and poor outcome. In addition, the present study showed that the mid-term outcome of all-comers was worse than the outcome of ACS patients in most randomized clinical trials and registry studies. A few aspects regarding the study need to be discussed.

The number of patients was small in substudy **I**. The study population was restricted to those with elevated troponin I levels, and patients with UA were excluded. In clinical practice, a minority of ACS patients with ST-segment depression and inverted or positive T waves presented without troponin elevation, at least before the recent introduction of the new sensitive troponin analyses.

Patients with ECG signs of LVH were excluded, because these patients may show persistent ST-segment depression, the "strain" pattern (**I and IV**). It would be important to evaluate the prognostic value of T-wave polarity also in patients with LVH. In one study in patients with symptoms suggestive of an ACS (n=5,324), those with ECG-LVH had approximately 3.5 times higher 30-day mortality than those without these ECG abnormalities (Pope et al. 2004). However, it was recently shown that LVH was associated with adverse prognostic factors in NSTE-ACS, but LVH provided no significant additional prognostic utility beyond comprehensive risk assessment using the GRACE score (Ali et al. 2011).

The definition of the T wave is somewhat disputable in patients with ST-segment deviation. In a recent statement by a working group, negative T waves were defined when the terminal portion of the T wave is below the isoelectric line (Nikus et al. 2010). In the present study, the T wave was

defined as positive or negative if it was 1 mm above or below the isoelectric line, measured more than 120 ms after the J point (**I-IV)**. Most investigators do not specifically report how they define the T-wave abnormalities – usually only the cut-off value and the definition of the isoelectric line are reported.

The ECG changes had to be recorded during anginal pain (**I**). In the vast majority of studies, the authors do not report whether the ECGs were recorded during symptoms or not. ECG signs of severe CAD may resolve within minutes with the disappearance of anginal symptoms and myocardial ischemia (Atie et al. 1991). It is important to report whether the ECG in a patient with ACS has been recorded during symptoms or not.

In the present study, ECG patterns were evaluated, while most investigators use quantitative measures of ECG signs of myocardial ischemia, like the degree of ST-segment deviation. It is proposed that recognizing certain high-risk ECG patterns will result in more accurate handling of the patients. However, the predictive value of ECG patterns and quantitative ST/T measures should be compared in future prospective studies.

Consecutive patients with ACS were included (**II and III**). After collecting AMI patients for 8 months, it was decided to also include patients with UA. Hence, the recruitment of patients with UA was shorter than for MI patients. To be able to study the relative distribution of all the 3 ACS categories, STEMI and NSTEMI patients were also included concurrently with the UA patients. As study inclusion was clinical – not investigational – coronary angiography was not performed on all patients.

It is a challenge to perform ACS studies with consecutive patients in busy emergency departments. For that reason, study inclusion and filling of study files were performed by the study nurses and the investigators, and were not left to the physicians working in the emergency department (**II-III**). Due to this fact, some parameters – such as Killip class and history of heart failure, which could have influenced outcome – could not be used in the statistical analyses.

Interestingly, this study showed a very similar MI incidence as the Swedish national registry (**II**). Calculating the observed MI cases in the present study and estimating the number of inhabitants in the study region at 340,000, the number of MIs was 20/10,000/y. The corresponding number for RIKS-HIA was 20.9/10,000/y (http://www.ucr.uu.se/rikshia/). This fact indicates robustness in patient inclusion in the present study, as RIKS-HIA is considered to be a high-class registry. In addition, of all AMI patients, the relative proportion of NSTEMI in the present study (64%) is fairly close to the ones from the Danish "real life" study (60%) and the Swedish national registry (71%), provided that LBBB-MI is classified as NSTEMI (Terkelsen et al. 2005); http://www.ucr.uu.se/rikshia/). The relative proportion of STEMI was higher in randomized controlled studies and many registry studies.

Study **IV** was retrospective and hence ECGs could not be found in some patients. Due to strict inclusion and exclusion criteria, only a minority of the original study population was included.

So far, there is no solid proof for the proposed patho/electrophysiologic background for the two main terms used in this thesis: regional and CSI. However, as shown in the review of the literature, there is a considerable amount of indirect evidence for the correlation between the ECG patterns and the proposed pathophysiologic substrate. Magnetic resonance imaging could be a potential method to study various ischemic phenomena, but the studies need to be done during the minutes or tens of minutes when the patients are symptomatic, which certainly poses a great logistic challenge. In particular, patients with CSI may be hemodynamically unstable – which makes magnetic resonance imaging even more challenging.

2. Outcome predictors in non-ST elevation acute coronary syndrome

2.1 Clinical markers

The present study verified the importance of many of the baseline parameters, which, in previous studies, have proven to have prognostic importance in NSTE-ACS patients and are used in the risk scores (**II**). The TIMI risk score for UA/NSTEMI and the GRACE risk score for in-hospital and six-month mortality are established and guideline-recommended tools for risk assessment (Antman et al. 2000; Granger et al. 2003). In the present study (**II**), age, initial serum creatinine level, and lower blood pressure at hospital admission were associated with increased mortality in multivariate analysis. These findings are in line with the observations from the large GRACE registry, from which the scoring systems have been developed. History of heart failure and heart rate at presentation, parameters that were not included in this study, are also included in the GRACE risk score parameters. However, diuretic use at admission, a probable marker of heart failure in many patients, emerged as a strong predictor of poor prognosis. History of MI, which is a GRACE risk score parameter, had prognostic impact in the univariate, but not in the multivariate analysis, of the present study. The exact explanation for the difference between the GRACE study population and the actual patient material in this respect is unknown. It has to be pointed out that this study included consecutive patients from one hospital, while registry studies could be more prone to under-reporting by individual participating centers (Armstrong 2002). Another explanation could be differences in the size of the study populations.

In summary, the present study verified the importance of established baseline risk markers in all-comers with ACS.

2.2 Acute coronary syndrome categories

This study showed that MI mortality was definitely higher than that reported in randomized clinical trials (**II**). Unadjusted in-hospital mortality in the whole study cohort was 10.4%, NSTEMI patients had the highest mortality (13%) compared with 9.6% for STEMI and 2.6% for UA. Mortality for

NSTEMI (27%) remained higher than for STEMI (19%), also at 10-month follow-up. In another all-comers' registry study, in-hospital mortality for NSTEMI patients was 13.3%, which is virtually identical to the findings of the present study (Terkelsen et al. 2005). Also, in a manner identical to the present study, the Danish investigators showed the highest mid-term (one-year) mortality of the three ACS categories for NSTEMI (30.5%).

In clinical trials, in-hospital mortality of STEMI patients has been around 5% (Andersen et al. 2003) (Topol and GUSTO V Investigators. 2001). Even at 30-days follow-up, mortality figures in the same range have been reported (Montalescot et al. 2011). Differences in age and co-morbidities, as well as strict inclusion and exclusion criteria and/or selection bias typical for randomized clinical trials, probably largely explain the differences.

In most published studies, lower in-hospital mortality has been reported for NSTEMI than for STEMI. In a Spanish registry, NSTEMI 28-day case fatality was lower than for STEMI patients (Garcia-Garcia et al. 2011). However, the multivariate adjusted seven-year mortality for 28-day survivors was higher for NSTEMI than for STEMI, and patients with unclassified MI (pacemaker ECG and LBBB) presented the highest short- and long-term mortality. In a large study of 4 registries of NSTE-ACS patients, in-hospital mortality was only 0.7% in patients enrolled in clinical trials, while non-participants had a 2.1% in-hospital mortality (p=001) (Hutchinson-Jaffe et al. 2010). The median age was 68 and 65 in non-enrolled and enrolled patients, respectively, while the patients in the present study were almost 10 years older (median age 75 y). One possible reason for the considerably higher mortality, and for the fact that the NSTEMI patients continued to have a high rate of fatal events compared with the STEMI patients, is under-reporting in registry studies. For example, in the GRACE registry, patients who expired within 24 hours of admission tended to be excluded (Armstrong 2002). The quality of registry studies is dependent on the reporting activity of the individual investigators in the participating centres. The fact that, in general, STEMI is easier to diagnose than NSTEMI, could be another reason for the outcome differences.

The rather low rate of invasive diagnostic evaluation and interventional therapy (24%) could be a possible explanation for the differences in outcome between the present study and registry or randomized clinical trials. Benefit from an early invasive strategy in NSTE-ACS was documented in the FRISC-II and Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) trials (Cannon et al. 2001a; Wallentin et al. 2000). Early interventional strategy was not fully implemented at the time of the studies (**II** and **III),** and primary PCI was not standard therapy in our hospital during the study period. Despite the relatively low rate of revascularization, there was a strong trend for PCI and CABG to have positive prognostic impact on mortality. Differences in age distribution between randomized trials and "real life" cohorts representing consecutive patients may also explain differences in revascularization rates. Clinicians may be reluctant to choose an invasive therapeutic strategy for older people, in whom data from randomized trials is scarce (Bhatt et al. 2004).

There are also differences between registry studies. In the National Registry of Myocardial Infarction 2-4 observational studies (n=255,256), in-hospital mortality rates were 15.8% for patients with ST-segment depression and 15.5% for those with ST-segment elevation or LBBB (Pitta et al. 2005). These numbers are actually somewhat higher than in the present study. Finally, one explanation for the difference in distribution of ACS categories may be the definition of ACS. Some studies used the initial diagnosis, while others used final ACS diagnosis.

In the present study, in-hospital mortality of patients in UA was only 2.6% (**II**). No additional deaths appeared for up to 6 months. The 28 day mortality rate of 2681 patients with UA in 5 Spanish registries, 2.2% in men (mean age 63.6 y) and 3.5% in women (mean age 68.6 y), was in the same range as in the present study (Marrugat et al. 2004).

In summary, the present study indicated high in-hospital and mid-term mortality of all-comers with ACS compared to previous reports from randomized clinical trial. The NSTEMI patients proved to have higher mortality rates than patients with STEMI and UA. Both absolute and relative

outcome measures from the three ACS categories were similar to another registry study from Denmark.

2.3 Severity of angiographic disease

In this study, in-hospital mortality (24%) was observed only in the patient group with the CSI ECG pattern, of whom all patients had severe triple vessel, LM or LM equivalent disease (**I**). In the group without mortality during the hospital stay, those with ECG signs of regional ischemia, 92% did not have severe CAD. In addition, in patients in the group with a higher proportion of severe CAD, clinical signs of heart failure were observed 10 times more often than in the patients with less severe disease.

It was recently shown that CAD severity correlates with outcome, despite improved anti-thrombotic and invasive therapeutic measures (Palmerini et al. 2011). Among NSTE-ACS patients, who underwent PCI, one-year mortality rates increased with increasing Syntax scores; mortality in the first, second and third tertiles were 1.5, 1.6 and 4%, respectively (p=0.0005). The Syntax score, which is a marker of angiographic disease severity, also proved to be an independent predictor of one-year death.

In summary, the patients with the CSI ECG pattern, all of whom had severe CAD, had high rates of heart failure and mortality during the hospital stay.

2.4 Conventional ECG changes associated with myocardial ischemia

The present paper reports the influence of seven pre-specified ECG patterns on patient outcome (**III**). Unadjusted in-hospital mortality rate was highest among patients with LBBB, CSI ECG and Q waves. The lowest mortality and the lowest incidence of in-hospital composite endpoints were observed in patients with LVH and other ST-segment depression and/or T-wave inversion.

In a recent registry study of NSTE-ACS, LVH was associated with adverse prognostic factors, including ST-segment depression, but did not provide any significant additional prognostic utility beyond comprehensive risk assessment, using the GRACE risk score (Ali et al. 2011). The authors proposed that the adverse prognosis associated with LVH in NSTE-ACS may be attributable to other prognosticators, such as ST-segment depression. In the present study, ST-segment depression and LVH were considered to be separate entities.

The negative prognostic impact of LBBB, which was evident from the present study, has been well-documented in the literature. In the Canadian ACS Registry (n=5003), 262 patients (5.2%) had LBBB (Baslaib et al. 2010). In-hospital and one-year mortality was significantly higher in patients with LBBB compared with QRS <120 milliseconds, and only LBBB was an independent predictor of one-year mortality (OR 1.93, 95% CI 1.28-2.90, p=0.002).

The negative prognostic impact of the presence, amplitude, and sum of ST-segment depression during an episode of ACS was proven in large trials published in the 1990s. At one-year follow-up in the TIMI registry, death or MI occurred in 11% of patients with 1 mm or more ST-segment deviation, compared with 6.8% of patients with new, isolated T-wave inversion and 8.2% of those with no ECG changes ($p<0.001$ when comparing ST- with no ST-segment deviation) (Cannon et al. 1997). Patients with only 0.5 mm ST-segment deviation showed a death or MI rate by one year of 16.3%, compared with 14.9, 9,7 and 6.1% in patients with ≥2 mm, ≥1 mm or no ST-segment deviation, respectively ($p<0.001$). On multivariate analysis, ST-segment deviation of either ≥1 mm or ≥0.5 mm remained independent predictors of death or MI by one year. Hyde et al showed that the degree of ST-segment depression predicted outcome; of patients with ≥2 mm ST-segment depression, four-year survival was only 53%, compared to 77% in those with 1-1.5 mm (<2 mm) and 82% in those with ≥0.5 mm (<1 mm) ($p<0.001$) (Hyde et al. 1999). However, a recent report questioned the importance of estimating the amount of ST-segment depression beyond simple dichotomous evaluation for the presence of ST-segment depression in NSTE-ACS (Yan et al.

2008). In direct comparison with the presence of ST-segment depression, quantitative analysis for cumulative ST-segment depression provided only similar incremental risk discrimination.

Also, the location of ST-segment depression affected outcome. Among patients with ST-segment deviation ≥1 mm, changes in the anterior leads carried the worst prognosis, with a rate of death or MI of 12.4% by one year, compared with 7 to 8% for other locations or no ST-segment deviation (p=0.002). Patients with ST-segment depression in the lateral leads were at higher risk for most in-hospital complications than patients with ST-segment depression not involving the lateral leads (Barrabes et al. 2000). Also, 30-day mortality rates were higher in the patients with than in those without lateral ST-segment depression (14.3 and 4.2%, respectively, p=0.007). Coronary angiography showed LM or triple vessel disease in 60% of patients with and 22% of those without lateral ST-segment depression (p<0.001).

In summary, previous studies have shown somewhat conflicting results regarding the prognostic significance of the amount of ST-segment depression, which was not a topic for the present study. Previous studies dealing with the location of ST-segment depression seem to be supported by the results of the present study. By definition, in the CSI ECG pattern, the maximal ST-segment depression is localized to the lateral precordial leads V4-V5.

2.4.1 Lead aVR ST-segment elevation

The importance of lead aVR ST-segment elevation was shown in NSTEMI patients, where the rates of in-hospital death in patients without and with 0.5 to 1 mm (n=116) or >1 mm (n=134) of ST-segment elevation in lead aVR were 1.3, 8.6, and 19.4%, respectively (p<0.001) (Barrabes et al. 2003). After adjustment for the baseline clinical predictors and for ST-segment depression on admission, the OR for death in the last two groups were 4.2 (95% CI, 1.5-12.2) and 6.6 (95% CI, 2.5-17.6), respectively. In a recent study, ST-segment depression plus ST-segment elevation in lead

aVR was a stronger independent predictor of cardiovascular death (HR 2.29, 95% CI 1.44 - 3.64, p<0.001) than isolated ST-segment deviation (HR 1.52, 95% CI 0.98 - 2.36, p=0.06) at one-year follow-up (Taglieri et al. 2011). The CSI ECG pattern used in the present study contains ST-segment elevation in lead aVR.

In summary, the CSI ECG pattern is unique in taking into consideration 3 important aspects of ECG changes in NSTE-ACS: ST-segment depression, T-wave inversion and lead aVR ST-segment elevation. If one takes only individual changes, such as ST-segment deviation or T-wave changes into consideration in risk association of the individual patient with NSTE-ACS, important diagnostic and prognostic "messages" in the ECG may be missed. A rethinking with the introduction of distinct high-risk ECG patterns is needed.

3. Predictive accuracy of the ECG pattern of circumferential subendocardial ischemia

The present series of experiments extend the pioneer work done by Sclarovsky and his co-workers during the 1980s and 1990s. The present study (**I, III)** confirms observations from a previous small study regarding the association of a distinct ECG pattern, the CSI ECG, with poor outcome. In NSTEMI patients without tachycardia, ST-segment depression and inverted T waves maximally in leads V4-V5, was associated with high in-hospital mortality. While patients with a positive T wave in the lead with ST-segment depression had no in-hospital mortality, those with inverted T waves had 24% mortality (p=0.02). The patients with inverted T waves had a ten-fold risk of heart failure during the hospital stay compared with those with positive T waves. The ECG pattern with ST-segment depression and inverted T waves maximally in leads V4-V5 from Study **I** can be considered as the same pattern as in Studies **III** and **IV.** A retrospective reanalysis of the ECGs

proved that all the patients with inverted T waves in Study **I** showed concomitant ≥0.5 mm ST-elevation in lead aVR. Regarding the definition of CSI, for studies **III** and **IV,** lead aVR ST-segment elevation (≥0.5 mm) was added to the definition and the number of leads with ST-segment depression was specified as six or more. These measures can be considered as fine-tuning towards the most clinically useful definition of the ECG pattern during the evolving process of establishing a high-risk ECG marker in NSTE-ACS.

The ECG pattern of CSI predicted a high rate (48%) of composite end-points at 10 months follow-up, compared to six other ECG categories. The present work (**III**) is the first large-scale study to show that also in multivariate analysis this ECG pattern was associated with a higher rate of composite end-points. In addition, studies **III-IV** included patients with tachycardia, which was an exclusion criterion in study **I**.

In one large multicentre randomized trial (N=6,770), the effect of location of ST-segment depression and T-wave polarity on one-year mortality in NSTE-ACS was reported (Atar et al. 2007). Patients with ST-segment depression and T-wave inversion in leads V4 to V6 had the highest one-year mortality rate of all groups, significantly higher compared with patients with ST-segment depression without T-wave inversion in those leads. In logistic regression analysis, ST-segment depression with T-wave inversion in leads V4 to V6 was an independent predictor of one-year mortality. Conversely, ST-segment depression without T-wave inversion in leads V4 to V6 or other ECG presentations were not independent predictors of high one-year mortality. When comparing this large study with the ECG patterns that were used in the present study (**III**), it is evident that patients with the CSI ECG pattern in the study by Atar et al were among those with high-risk of one-year mortality, but it is likely that this group also contained some patients who were classified as “other ST-segment depression and/or T-inversion”. Hence, direct comparison of the study results is not possible.

In summary, in the present study – for the first time – the negative prognostic impact of the CSI ECG pattern is shown in a large-scale patient population of all-comers with ACS.

4. The ECG pattern of circumferential subendocardial ischemia and angiographic findings

As pointed out in the review of the literature, lesion severity as expressed by coronary angiography will affect the outcome in NSTE-ACS. In the ACUITY trial, lesion severity provided important added independent predictive value for 30-day and one-year ischemic outcomes, beyond the well-recognized clinical risk factors (Lansky et al. 2010). It was also shown that an invasive treatment strategy with PCI or CABG improves outcome in high-risk patients with ACS (Diderholm et al. 2002). LM disease puts the ACS patient at a very high risk for adverse outcome. However, with invasive treatment, mortality has also been reduced in this high-risk group. All-cause mortality at 6 months was 6% with PCI, which is definitely lower than that expected from data on the natural course of LM disease in general (three-year survival <50-75%) (Amanullah et al. 1999). Accordingly, it is crucial to identify ACS patients who have high probability for LM disease by non-invasive methods – such as the ECG – for appropriate management.

The present study of NSTEMI patients with transient ST-segment depression during pain showed that all patients with the CSI ECG pattern had severe triple vessel, LM or LM equivalent disease (**I**). In addition, all patients with severe triple vessel disease presented with this ECG pattern. The PPVs and NPVs for this ECG pattern to predict LM, LM equivalent or severe triple vessel disease in coronary angiography were 100 and 92%, respectively. In all-comers with ACS, 71% of the patients with the CSI ECG pattern had triple vessel disease and, in addition, LM disease, either isolated or in association with single, double or triple vessel disease, was present in 25% of the patients (**III**). The corresponding numbers for the ECG pattern of other ST-segment depression and/or T-wave inversion was only 22% for triple vessel and 3% for LM disease. Finally, in patients

having CABG, the present study showed that the CSI ECG pattern during anginal pain was found in 61 of 80 patients (76%) with LM disease and in 12 of 65 patients (19%) without LM disease (**IV**). The CSI ECG pattern had a sensitivity of 76% and a specificity of 81% to predict significant LM stenosis on angiography.

In summary, the present study has established the association between the CSI ECG pattern and severe CAD including LM disease. Patients with other ST-segment depression with or without T-wave changes proved to have relatively milder degrees of angiographic stenosis. Based on the findings in this thesis, in patients with the CSI ECG pattern, urgent invasive evaluation should be considered.

5. Pathophysiological mechanisms of circumferential subendocardial ischemia

The present study did not aim at studying the pathophysiologic mechanisms of CSI. Actually, there are no studies explicitly addressing this issue. However, as pointed out in the review of the literature, there is a lot of indirect evidence both from experimental and human studies for the hypothesis that the CSI ECG pattern is induced by a large area of subendocardial ischemia of the LV. In animals, inducing acute global myocardial ischemia resulted in a significant rise in LV end-diastolic pressure (Palacios et al. 1976). Reduction in coronary flow in the subendocardium of the LV shifts the electrical vector from the epicardium towards the subendocardium, which induces mainly ST-segment depression when recorded by precordial electrodes in the surface ECG (Guyton et al. 1977). In autopsy cases with involvement of the entire subendocardial circumference from apex to base of the LV, the premortal ECGs showed ST-segment depression accompanied by a diphasic or inverted T wave (Myers et al. 1951). Postmortem coronary angiography has shown severe disease in patients, who had shown severe ST-segment depression in many leads before

death and who were found to have large subendocardial infarctions which were circumferential or nearly circumferential in extent at autopsy (Ogawa et al. 1985). Body surface potential mapping during acute reversible myocardial ischemia showed that, irrespective of the location of ischemia within the myocardium, the optimal location for ST-segment depression was close to leads V5 and V6. Reciprocal ST-segment elevation was found over the right shoulder, which in 12-lead ECG is represented by lead aVR (Hänninen et al. 2001).

The present study adds to the current knowledge that patients presenting with the CSI ECG pattern have more severe disease on coronary angiography, more heart failure during the hospital stay, higher in-hospital mortality, and higher risk for adverse outcome during mid-term follow-up (**I, III**) than patients with other ECG patterns. No specific culprit artery or culprit lesion that would be typical for the patients, who present with the CSI ECG pattern, has been found. The patients have mostly shown total or sub-total LM or LM equivalent obstruction, triple or double vessel disease.

In summary, a large area of myocardial ischemia is the main pathophysiological background for the CSI ECG pattern. It is difficult to find other logical explanations for the distinct ECG changes present in these cases.

6. Major findings of the study

6.1 Poor outcome in real life non-ST elevation acute coronary syndrome patients

In a series of 1,188 unselected, prospectively collected, consecutive ACS patients from the Tampere University Hospital, in-hospital mortality was 9.6, 13 and 2.6% ($p < 0.001$) and mortality at a median follow-up of 10 months 19, 27 and 12% ($p<0.001$), for STEMI, NSTEMI and UA, respectively **(II)**. Mortality in this "real life" cohort was clearly higher than in randomized clinical

trials, in which younger, proportionately more male patients with fewer co-morbidities are included. Even in registry studies, under-reporting may exclude critically ill patients, resulting in seemingly low mortality figures. Absolute and relative mortality figures are heavily dependent on the reporting activity, and inclusion and exclusion criteria of the different studies.

6.2 An ECG marker of severe coronary artery disease in non-ST elevation acute coronary syndrome

The ECG pattern of CSI was associated with severe CAD, high in-hospital mortality and risk for heart failure **(I)**. The CSI ECG pattern predicted a high rate (48%) of composite end-points at 10 months follow-up compared with six other ECG categories **(III)**. Also in multivariate analysis, the CSI ECG pattern was independently associated with a higher rate of composite end-points. Mortality of LM disease is high. According to the present study, high-risk NSTE-ACS individuals with LM disease can be identified with the CSI ECG pattern.

6.3 Impact of the present study on current treatment strategies

ST-segment deviation and elevated levels of biochemical markers are among the known high-risk parameters in NSTE-ACS. Invasive evaluation should be performed within 24 hours in NSTE-ACS patients with high-risk features. The present findings suggest that a sub-group of patients with a specific ECG pattern in the clinical setting of NSTE-ACS should have high priority for invasive evaluation without delay. Three-quarters of the patients with the CSI ECG pattern needed CABG, compared to one-fifth of the patients with ECG signs of regional subendocardial ischemia **(I)**. The patients with the CSI ECG pattern should have close surveillance for possible clinical deterioration.

Clopidogrel and prasugrel should probably be avoided as anti-thrombotic agents, due to the possibility of emergent or urgent CABG.

Based on the findings in this thesis, it may be concluded that patients presenting with a clinical picture consistent with ACS and the slightest signs of hemodynamic compromise in combination with the CSI ECG pattern should be handled as STEMI cases with emergent coronary angiography. However, large-scale prospective studies of consecutive patients with ACS are probably needed before this recommendation can be implemented into ACS guidelines.

SUMMARY AND CONCLUSIONS

The principal findings and conclusions are:

1. A distinct CSI ECG pattern, ST depression ≥0.5 mm in ≥6 leads, maximally in leads V4-V5 with inverted T waves and ST elevation ≥0.5 mm in lead aVR, is a marker of a high-risk NSTE-ACS subgroup, predicting severe CAD, high rates of heart failure and mortality during the hospital stay, when compared with other ECG patterns in patients with ACS (**I**).

2. Mortality of patients with MI – especially those classified as NSTEMI – is high in unselected "real life" patient cohorts, compared with randomized clinical trials or registry studies (**II**).

3. In all-comers with ACS, the CSI ECG pattern was present in 8% of the patients. The CSI ECG pattern predicted a significantly higher rate of composite endpoints at mid-term follow-up compared to all the other ECG categories. In multivariate analysis, the CSI ECG pattern was identified as an independent predictor for poor prognosis (**III**).

4. The ECG pattern of CSI is strongly associated with angiographic LM disease in patients who undergo urgent or emergent CABG - the CSI ECG pattern had a sensitivity of 76% and a specificity of 81% to predict significant LM stenosis on angiography (**IV**).

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REFERENCES

Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB trial. Thrombolysis In Myocardial Ischemia (1994): Circulation 89:1545-1556.

Early effects of tissue-type plasminogen activator added to conventional therapy on the culprit coronary lesion in patients presenting with ischemic cardiac pain at rest. Results of the Thrombolysis In Myocardial Ischemia (TIMI IIIA) trial (1993): Circulation 87:38-52.

The BARI protocol. Protocol for the Bypass Angioplasty Revascularization Investigation (1991): Circulation 84 (Suppl 5):V1.

Prospective randomised study of coronary artery bypass surgery in stable angina pectoris. Second interim report by the European Coronary Surgery Study (ECSS) Group (1980): Lancet 2:491-495.

Agetsuma H, Hirai M, Hirayama H, Suzuki A, Takanaka C, Yabe S, Inagaki H, Takatsu F, Hayashi H, and Saito H (1996): Transient giant negative T wave in acute anterior myocardial infarction predicts R wave recovery and preservation of left ventricular function. Heart 75:229-234.

Ali S, Goodman SG, Yan RT, Budaj A, Fox KA, Gore JM, Brieger D, Lopez-Sendon J, Langer A, van de Werf F, Steg PG, and Yan AT (2011): Prognostic significance of electrocardiographic-determined left ventricular hypertrophy and associated ST-segment depression in patients with non-ST-elevation acute coronary syndromes. Am Heart J 161:878-885.

Alpert JS, Thygesen K, Antman E, and Bassand JP (2000): Myocardial infarction redefined--a consensus document of the joint European Society of Cardiology/American College of Cardiology committee for the redefinition of myocardial infarction. J Am Coll Cardiol 36:959-969.

Amanullah AM, Heo J, Acio E, Narula J, and Iskandrian AE (1999): Predictors of outcome of medically treated patients with left main/three-vessel coronary artery disease by coronary angiography. Am J Cardiol 83:445-8, A9.

Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, Abildgaard U, Pedersen F, Madsen JK, Grande P, Villadsen AB, Krusell LR, Haghfelt T, Lomholt P, Husted SE, Vigholt E, Kjaergard HK, Mortensen LS, and DANAMI-2 Investigators (2003): A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med 349:733-742.

Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, and Braunwald E (2000): The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 284:835-842.

Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC,Jr, Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, and Ornato JP (2004): ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). J Am Coll Cardiol 44:E1-E211.

Armstrong PW (2002): Coronary reperfusion: Numerators searching for denominators. Lancet 359:371-372.

Arnett EN, Isner JM, Redwood DR, Kent KM, Baker WP, Ackerstein H, and Roberts WC (1979): Coronary artery narrowing in coronary heart disease: Comparison of cineangiographic and necropsy findings. Ann Intern Med 91:350-356.

Assali A, Sclarovsky S, Herz I, Vaturi M, Gilad I, Solodky A, Zafrir N, Adler Y, Sagie A, Birnbaum Y, and Hasdai D (2000): Persistent ST segment depression in precordial leads V5-V6 after Q-wave anterior wall myocardial infarction is associated with restrictive physiology of the left ventricle. J Am Coll Cardiol 35:352-357.

Atar S, Fu Y, Wagner GS, Rosanio S, Barbagelata A, and Birnbaum Y (2007): Usefulness of ST depression with T-wave inversion in leads V4 to V6 for predicting one-year mortality in non-ST-elevation acute coronary syndrome (from the electrocardiographic analysis of the Global Use of Strategies To Open occluded coronary arteries IIB trial). Am J Cardiol 99:934-938.

Atie J, Brugada P, Brugada J, Smeets JL, Cruz FE, Roukens MP, Gorgels A, Bar FW, and Wellens HJ (1991): Clinical presentation and prognosis of left main coronary artery disease in the 1980s. Eur Heart J 12:495-502.

Baroldi G and Scomazzoni G (1967): Coronary circulation in the normal heart. Coronary arteries. In: Coronary circulation in the normal and the pathologic heart, pp. 5-19. Eds. Baroldi G and Scomazzoni G, Office of the surgeon general. Department of the Army. Washington, D.C., U.S.

Barrabes JA, Figueras J, Moure C, Cortadellas J, and Soler-Soler J (2000): Prognostic significance of ST segment depression in lateral leads I, aVL, V5 and V6 on the admission electrocardiogram in patients with a first acute myocardial infarction without ST segment elevation. J Am Coll Cardiol 35:1813-1819.

Barrabes JA, Figueras J, Moure C, Cortadellas J, and Soler-Soler J (2003): Prognostic value of lead aVR in patients with a first non-ST-segment elevation acute myocardial infarction. Circulation 108:814-819.

Baslaib F, Alkaabi S, Yan AT, Yan RT, Dorian P, Nanthakumar K, Casanova A, Goodman SG, and Canadian Acute Coronary Syndrome Registry Investigators (2010): QRS prolongation in patients with acute coronary syndromes. Am Heart J 159:593-598.

Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W, ESC Committee for Practice Guidelines (CPG), Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Kristensen SD, Widimsky P, McGregor K, Sechtem U, Tendera M, Hellemans I, Gomez JL, Silber S, Funck-Brentano C, Kristensen SD, Andreotti F, Benzer W, Bertrand M, Betriu A, De Caterina R, DeSutter J, Falk V, Ortiz AF, Gitt A, Hasin Y, Huber K, Kornowski R, Lopez-Sendon J, Morais J, Nordrehaug JE, Silber S, Steg PG, Thygesen K, Tubaro M, Turpie AG, Verheugt F, Windecker S, and Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology (2007): Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The task force for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes of the European Society of Cardiology. Eur Heart J 28:1598-1660.

Bayes de Luna A, Wagner G, Birnbaum Y, Nikus K, Fiol M, Gorgels A, Cinca J, Clemmensen PM, Pahlm O, Sclarovsky S, Stern S, Wellens H, Zareba W, and International Society for Holter and Noninvasive Electrocardiography (2006): A new terminology for left ventricular walls and location of myocardial infarcts that present Q wave based on the standard of cardiac magnetic resonance imaging: A statement for healthcare professionals from a committee appointed by the International Society for Holter and Noninvasive Electrocardiography. Circulation 114:1755-1760.

Bayley RH (1946): The electrocardiographic effects of injury at the endocardial surface of the left ventricle. Am Heart J 31:677-684.

Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, Greenbaum AB, Berger PB, Cannon CP, Cohen DJ, Gibson CM, Saucedo JF, Kleiman NS, Hochman JS, Boden WE, Brindis RG, Peacock WF, Smith SC,Jr, Pollack CV,Jr, Gibler WB, Ohman EM, and CRUSADE Investigators (2004):Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: Results from the CRUSADE quality improvement initiative. JAMA 292:2096-2104.

Birnbaum Y, Sclarovsky S, Mager A, Strasberg B, and Rechavia E (1993): ST segment depression in a VL: A sensitive marker for acute inferior myocardial infarction. Eur Heart J 14:4-7.

Birnbaum Y, Herz I, Sclarovsky S, Zlotikamien B, Chetrit A, Olmer L, and Barbash GI (1996): Prognostic significance of precordial ST segment depression on admission electrocardiogram in patients with inferior wall myocardial infarction. J Am Coll Cardiol 28:313-318.

Blumgart HL, Schlesinger MJ, and Zoll PM (1941): Angina pectoris, coronary failure and myocardial infarction. The role of coronary occlusions and collateral circulation. JAMA 116:91-97.

Boyd LJ and Scherf D (1940): The electrocardiogram after mechanical injury of the inner surface of the heart. Bull New York Med College 3:1-21.

Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE,3rd, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC,Jr, and American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina) (2002): ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--2002: Summary article: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee on the management of patients with unstable angina). Circulation 106:1893-1900.

Bulkley BH, Roberts WC (1976): Atherosclerotic narrowing of the left main coronary artery. A necropsy analysis of 152 patients with fatal coronary heart disease and varying degrees of left main narrowing. Circulation 53:823-828.

Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, Pearce DJ, Diver DJ, Kells C, Feldman T, Williams M, Gibson RS, Kronenberg MW, Ganz LI, Anderson HV, and Braunwald E (1997): The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: Results of the TIMI III registry ECG ancillary study. Thrombolysis In Myocardial Ischemia. J Am Coll Cardiol 30:133-140.

Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E, and TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)--Thrombolysis in Myocardial Infarction 18 Investigators. (2001a): Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879-1887.

Cannon CP, Battler A, Brindis RG, Cox JL, Ellis SG, Every NR, Flaherty JT, Harrington RA, Krumholz HM, Simoons ML, Van De Werf FJ, Weintraub WS, Mitchell KR, Morrisson SL, Brindis RG, Anderson HV, Cannom DS, Chitwood WR, Cigarroa JE, Collins-Nakai RL, Ellis SG, Gibbons RJ, Grover FL, Heidenreich PA, Khandheria BK, Knoebel SB, Krumholz HL, Malenka DJ, Mark DB, Mckay CR, Passamani ER, Radford MJ, Riner RN, Schwartz JB, Shaw RE, Shemin RJ, Van Fossen DB, Verrier ED, Watkins MW, Phoubandith DR, and Furnelli T (2001b): American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology task force on clinical data standards (acute coronary syndromes writing committee). J Am Coll Cardiol 38:2114-2130.

Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, and Chaitman BR (1995): Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. Circulation 91:2335-2344.

Challa PK, Smith KM, and Conti CR (2007): Initial presenting electrocardiogram as determinant for hospital admission in patients presenting to the emergency department with chest pain: A pilot investigation. Clin Cardiol 30:558-561.

Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, and Ludbrook P (1987): Thrombolysis In Myocardial Infarction (TIMI) trial, phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 76:142-154.

Cheung SC, Chan CW (2011): Cardiac magnetic resonance imaging: Choice of the year: Which imaging modality is best for evaluation of myocardial ischemia? (MRI-side). Circ J 75:724-30; discussion 723.

de Bruyne B, and Sarma J (2008). Fractional flow reserve: a review. Heart 94:949-959.

De Chantal M, Diodati JG, Nasmith JB, Amyot R, Leblanc AR, Schampaert E, and Pharand C (2006): Progressive epicardial coronary blood flow reduction fails to produce ST-segment depression at normal heart rates. Am J Physiol Heart Circ Physiol 291:H2889-2896 .

de Feyter PJ, Serruys PW (1984): Thrombolysis of acute total occlusion of the left main coronary artery in evolving myocardial infarction. Am J Cardiol 53:1727-1728.

de Lemos JA, Blazing MA, Wiviott SD, Brady WE, White HD, Fox KA, Palmisano J, Ramsey KE, Bilheimer DW, Lewis EF, Pfeffer M, Califf RM, Braunwald E, and A to Z Investigators. (2004): Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: Results from the A phase of the A-to-Z trial. Eur Heart J 25:1688-1694.

De Servi S, Specchia G, and Angoli L (1979): Coronary artery spasm of different degrees as cause of angina at rest with ST segment depression and elevation. Br Heart J 42:110-112.

de Zwaan C, Bar FW, and Wellens HJ (1982): Characteristic electrocardiographic pattern indicating a critical stenosis high in left anterior descending coronary artery in patients admitted because of impending myocardial infarction. Am Heart J 103:730-736.

DeMots H, Rosch J, McAnulty JH, and Rahimtoola SH (1977): Left main coronary artery disease. Cardiovasc Clin 8:201-211.

Diderholm E, Andren B, Frostfeldt G, Genberg M, Jernberg T, Lagerqvist B, Lindahl B, and Wallentin L (2002): ST depression in ECG at entry indicates severe coronary lesions and large benefits of an early invasive treatment strategy in unstable coronary artery disease; the FRISC II ECG substudy. The Fast Revascularisation during InStability in Coronary artery disease. Eur Heart J 23:41-49.

Doevendans PA, Gorgels AP, van der Zee R, Partouns J, Bar FW, and Wellens HJ (1995): Electrocardiographic diagnosis of reperfusion during thrombolytic therapy in acute myocardial infarction. Am J Cardiol 75:1206-1210.

Emond M, Mock MB, Davis KB, Fisher LD, Holmes DR,Jr, Chaitman BR, Kaiser GC, Alderman E, and Killip T,3rd (1994): Long-term survival of medically treated patients in the coronary artery surgery study (CASS) registry. Circulation 90:2645-2657.

Engelen DJ, Gorgels AP, Cheriex EC, De Muinck ED, Ophuis AJ, Dassen WR, Vainer J, van Ommen VG, and Wellens HJ (1999): Value of the electrocardiogram in localizing the occlusion site in the left anterior descending coronary artery in acute anterior myocardial infarction. J Am Coll Cardiol 34:389-395.

Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, Daly C, De Backer G, Hjemdahl P, Lopez-Sendon J, Marco J, Morais J, Pepper J, Sechtem U, Simoons M, Thygesen K, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology, and ESC Committee for Practice Guidelines (CPG) (2006):Guidelines on the management of stable angina pectoris: Executive summary: The task force on the management of stable angina pectoris of the European Society of Cardiology. Eur Heart J 27:1341-1381.

Freeman MR, Williams AE, Chisholm RJ, and Armstrong PW (1989): Intracoronary thrombus and complex morphology in unstable angina. Relation to timing of angiography and in-hospital cardiac events. Circulation 80:17-23.

Froelicher VF and Myers JN (2000): Diagnostic application of exercise testing. In: Exercise and the heart, pp. 161-208. Eds. Froelicher VF and Myers JN, W.B. Saunders Co, Philadelphia, U.S.

Garcia-Garcia C, Subirana I, Sala J, Bruguera J, Sanz G, Valle V, Aros F, Fiol M, Molina L, Serra J, Marrugat J, and Elosua R (2011): Long-term prognosis of first myocardial infarction according to the electrocardiographic pattern (ST elevation myocardial infarction, non-ST elevation myocardial infarction and non-classified myocardial infarction) and revascularization procedures. Am J Cardiol 108:1061-1067.

Goldberg S, Grossman W, Markis JE, Cohen MV, Baltaxe HA, and Levin DC (1978): Total occlusion of the left main coronary artery. A clinical, hemodynamic and angiographic profile. Am J Med 64:3-8.

Goodman SG, Fu Y, Langer A, Barr A, Tan M, Wagner GS, Barbagelata A, Sgarbossa EB, Birnbaum Y, Granger CB, Califf RM, Van de Werf F, Topol EJ, Armstrong PW, and GUSTO-IIb Investigators (2006): The prognostic value of the admission and predischarge electrocardiogram in acute coronary syndromes: The GUSTO-IIb ECG core laboratory experience. Am Heart J 152:277-284.

Goodman SG, Huang W, Yan AT, Budaj A, Kennelly BM, Gore JM, Fox KA, Goldberg RJ, Anderson FA,Jr, and Expanded Global Registry of Acute Coronary Events (GRACE2) Investigators (2009): The expanded global registry of acute coronary events: Baseline characteristics, management practices, and hospital outcomes of patients with acute coronary syndromes. Am Heart J 158:193-201.e1-5.

Gorgels AP, Vos MA, Mulleneers R, de Zwaan C, Bar FW, and Wellens HJ (1993): Value of the electrocardiogram in diagnosing the number of severely narrowed coronary arteries in rest angina pectoris. Am J Cardiol 72:999-1003.

Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA, and Global Registry of Acute Coronary Events Investigators. (2003): Predictors of hospital mortality in the Global Registry of Acute Coronary Events. Arch Intern Med 163:2345-2353.

Grossman W. (1986): Assessment of regional myocardial function. J Am Coll Cardiol 7:327-328.

Gruberg L, Sudarsky D, Kerner A, Hammerman H, Kapeliovich M, and Beyar R (2008): Troponin-positive, CK-MB-negative acute myocardial infarction: Clinical, electrocardiographic and angiographic characteristics. J Invasive Cardiol 20:125-128.

Guyton RA, McClenathan JH, Newman GE, and Michaelis LL (1977): Significance of subendocardial S-T segment elevation caused by coronary stenosis in the dog. Epicardial S-T segment depression, local ischemia and subsequent necrosis. Am J Cardiol 40:373-380.

Hackel DB, Wagner GS (1992): Acute circumferential subendocardial infarction. Clin Cardiol 15:373-376.

Haines DE, Raabe DS, Gundel WD, and Wackers FJ (1983): Anatomic and prognostic significance of new T-wave inversion in unstable angina. Am J Cardiol 52:14-18.

Hänninen H, Takala P, Mäkijärvi M, Korhonen P, Oikarinen L, Simelius K, Nenonen J, Katila T, and Toivonen L (2001): ST-segment level and slope in exercise-induced myocardial ischemia evaluated with body surface potential mapping. Am J Cardiol 88:1152-1156.

Hasdai D, Birnbaum Y, Herz I, Sclarovsky S, Mazur A, and Solodky A (1995): ST segment depression in lateral limb leads in inferior wall acute myocardial infarction. Implications regarding the culprit artery and the site of obstruction. Eur Heart J 16:1549-1553.

Hayden GE, Brady WJ, Perron AD, Somers MP, and Mattu A (2002): Electrocardiographic T-wave inversion: Differential diagnosis in the chest pain patient. Am J Emerg Med 20:252-262.

Hennings JR, Fesmire FM (2011): A new electrocardiographic criteria for emergent reperfusion therapy. Am J Emerg Med Epub ahead of print.

Herz I, Birnbaum Y, Zlotikamien B, Strasberg B, Sclarovsky S, Chetrit A, Wagner GS, and Barbash GI (1999): The prognostic implications of negative T waves in the leads with ST segment elevation on admission in acute myocardial infarction. Cardiology 92:121-127.

Hiss RG, Lamb LE, and Allen MF (1960): Electrocardiographic findings in 67,375 asymptomatic subjects. X. Normal values. Am J Cardiol 6:200-231.

Hlaing T, DiMino T, Kowey PR, and Yan GX (2005): ECG repolarization waves: Their genesis and clinical implications. Ann Noninvasive Electrocardiol 10:211-223.

Holmvang L, Clemmensen P, Lindahl B, Lagerqvist B, Venge P, Wagner G, Wallentin L, and Grande P (2003): Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. J Am Coll Cardiol 41:905-915.

Hurst JW (2007): Thoughts about the abnormalities in the electrocardiogram of patients with acute myocardial infarction with emphasis on a more accurate method of interpreting S-T segment displacement: Part II. Clin Cardiol 30:443-449.

Hutchinson-Jaffe AB, Goodman SG, Yan RT, Wald R, Elbarouni B, Rose B, Eagle KA, Lai CC, Baer C, Langer A, Yan AT, and Canadian Acute Coronary Syndromes (ACS) Registry I and II Investigators and Canadian Global Registry of Acute Coronary Events (GRACE/GRACE 2) Investigators (2010): Comparison of baseline characteristics, management and outcome of patients with non-ST-segment elevation acute coronary syndrome in versus not in clinical trials. Am J Cardiol 106:1389-1396.

Hyde TA, French JK, Wong CK, Straznicky IT, Whitlock RM, and White HD (1999): Four-year survival of patients with acute coronary syndromes without ST-segment elevation and prognostic significance of 0.5-mm ST-segment depression. Am J Cardiol 84:379-385.

James TN. (1960): The arteries of the free ventricular walls in man. Anat Rec 136:371-384.

Kattainen A, Salomaa V, Härkänen T, Jula A, Kaaja R, Kesäniemi YA, Kähonen M, Moilanen L, Nieminen MS, Aromaa A, and Reunanen A (2006): Coronary heart disease: From a disease of middle-aged men in the late 1970s to a disease of elderly women in the 2000s. Eur Heart J 27:296-301.

Katz AM (2006): The ischemic heart. In: Physiology of the heart, pp. 522-545. Ed. Katz AM, Lippincott Williams & Wilkins, Philadelphia, U.S.

Kaul P, Fu Y, Chang WC, Harrington RA, Wagner GS, Goodman SG, Granger CB, Moliterno DJ, Van de Werf F, Califf RM, Topol EJ, Armstrong PW, and PARAGON-A and GUSTO IIb Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network (2001): Prognostic value of ST segment depression in acute coronary syndromes: Insights from PARAGON-A applied to GUSTO-IIb. PARAGON-A and GUSTO IIb investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network. J Am Coll Cardiol 38:64-71.

Kemball Price R, Janes LR (1943): A case of subendocardial infarction. Br Heart J 5:134-138.

Kisch B, Nahum L, and Hoff H (1940): Predominance of surface over deep cardiac injury in producing changes in the electrocardiogram. Am Heart J 20:174-190.

Kosuge M, Kimura K, Ishikawa T, Ebina T, Shimizu T, Hibi K, Toda N, Tahara Y, Tsukahara K, Kanna M, Okuda J, Nozawa N, Ozaki H, Yano H, and Umemura S (2005): Predictors of left main or three-vessel disease in patients who have acute coronary syndromes with non-ST-segment elevation. Am J Cardiol 95:1366-1369.

Ladich E, Burke AP, Joner M, Kolodgie F, Kutys R, and Virmani R (2006): Pathology of the left main coronary artery. In: Handbook of left main stem disease, pp. 1-26. Eds. Park S-J and Mintz GS, Informa healthcare, Oxfordshire, UK.

Lamfers EJ, Hooghoudt TE, Hertzberger DP, Schut A, Stolwijk PW, and Verheugt FW (2003): Abortion of acute ST segment elevation myocardial infarction after reperfusion: Incidence, patients' characteristics, and prognosis. Heart 89:496-501.

Lansky AJ, Goto K, Cristea E, Fahy M, Parise H, Feit F, Ohman EM, White HD, Alexander KP, Bertrand ME, Desmet W, Hamon M, Mehran R, Moses J, Leon M, and Stone GW (2010): Clinical and angiographic predictors of short- and long-term ischemic events in acute coronary syndromes: Results from the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial. Circ Cardiovasc Interv 3:308-316.

Leaman DM, Brower RW, Meester GT, Serruys P, and van den Brand M (1981): Coronary artery atherosclerosis: Severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 63:285-299.

Levine HD, Ford RV (1950): Subendocardial infarction; report of six cases and critical survey of the literature. Circulation 1:246-263.

Lim JS, Proudfit WL, and Sones FM, Jr (1975): Left main coronary arterial obstruction: Long-term follow-up of 141 nonsurgical cases. Am J Cardiol 36:131-135.

Lin KB, Shofer FS, McCusker C, Meshberg E, and Hollander JE (2008): Predictive value of T-wave abnormalities at the time of emergency department presentation in patients with potential acute coronary syndromes. Acad Emerg Med 15:537-543.

Marrugat J, Garcia M, Elosua R, Aldasoro E, Tormo MJ, Zurriaga O, Aros F, Masia R, Sanz G, Valle V, Lopez De Sa E, Sala J, Segura A, Rubert C, Moreno C, Cabades A, Molina L, Lopez-Sendon JL, Gil M, IBERICA Investigators, PRIAMHO Investigators, RESCATE Investigators, PEPA Investigators, and REGICOR Investigators (2004): Short-term (28 days) prognosis between genders according to the type of coronary event (Q-wave versus non-Q-wave acute myocardial infarction versus unstable angina pectoris). Am J Cardiol 94:1161-1165.

Maseri A, Parodi O, Severi S, and Pesola A (1976): Transient transmural reduction of myocardial blood flow demonstrated by thallium-201 scintigraphy, as a cause of variant angina. Circulation 54:280-288.

Maseri A, Pesola A, Marzilli M, Severi S, Parodi O, L'Abbate A, Ballestra AM, Maltinti G, De Nes DM, and Biagini A (1977): Coronary vasospasm in angina pectoris. Lancet 1:713-717.

Maseri A, Severi S, Nes MD, L'Abbate A, Chierchia S, Marzilli M, Ballestra AM, Parodi O, Biagini A, and Distante A (1978): "Variant" angina: One aspect of a continuous spectrum of vasospastic myocardial ischemia. Pathogenetic

mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. Am J Cardiol 42:1019-1035.

Min SY, Park DW, Yun SC, Kim YH, Lee JY, Kang SJ, Lee SW, Lee CW, Kim JJ, Park SW, and Park SJ (2010): Major predictors of long-term clinical outcomes after coronary revascularization in patients with unprotected left main coronary disease: Analysis from the MAIN-COMPARE study. Circ Cardiovasc Interv 3:127-133.

Mizuno K, Satomura K, Miyamoto A, Arakawa K, Shibuya T, Arai T, Kurita A, Nakamura H, and Ambrose JA (1992): Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. N Engl J Med 326:287-291.

Montalescot G, Zeymer U, Silvain J, Boulanger B, Cohen M, Goldstein P, Ecollan P, Combes X, Huber K, Pollack C, Jr, Benezet JF, Stibbe O, Filippi E, Teiger E, Cayla G, Elhadad S, Adnet F, Chouihed T, Gallula S, Greffet A, Aout M, Collet JP, Vicaut E, and ATOLL Investigators (2011): Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: The international randomised open-label ATOLL trial. Lancet 378:693-703.

Myers GB, Sears CH, and Hiratzka T (1951): Correlation of electrocardiographic and pathologic findings in ring-like subendocardial infarction of the left ventricle. Am J Med Sci 222:417-428.

Nikus K, Pahlm O, Wagner G, Birnbaum Y, Cinca J, Clemmensen P, Eskola M, Fiol M, Goldwasser D, Gorgels A, Sclarovsky S, Stern S, Wellens H, Zareba W, and de Luna AB (2010): Electrocardiographic classification of acute coronary syndromes: A review by a committee of the International Society for Holter and Non-invasive Electrocardiology. J Electrocardiol 43:91-103.

Nikus KC (2011): Coronary angiography. In: Multimodal cardiovascular imaging. Principles and applications, pp. 71-80. Eds. Pahlm O and Wagner GS, McGraw-Hill C, New York, U.S.

Noble RJ, Rothbaum DA, Knoebel SB, McHenry PL, and Anderson GJ (1976): Normalization of abnormal T waves in ischemia. Arch Intern Med 136:391-395.

Norman JE, Jr, Levy D (1995): Improved electrocardiographic detection of echocardiographic left ventricular hypertrophy: Results of a correlated data base approach. J Am Coll Cardiol 26:1022-1029.

Ogawa H, Hiramori K, Haze K, Saito M, Sumiyoshi T, Fukami K, Goto Y, and Ikeda M (1985): Classification of non-Q-wave myocardial infarction according to electrocardiographic changes. Br Heart J 54:473-478.

Owens CG, Adgey AA (2006): Electrocardiographic diagnosis of non-ST-segment elevation acute coronary syndromes: Current concepts for the physician. J Electrocardiol 39:271-274.

Palacios I, Johnson RA, Newell JB, and Powell WJ, Jr (1976): Left ventricular end-diastolic pressure volume relationships with experimental acute global ischemia. Circulation 53:428-436.

Palmerini T, Sangiorgi D, Marzocchi A, Tamburino C, Sheiban I, Margheri M, Vecchi G, Sangiorgi G, Franco N, Bartorelli A, Briguori C, Vignali L, Di Pede F, Ramondo A, Medda M, De Carlo M, Bolognese L, Benassi A, Palmieri C, Filippone V, Lauria G, and De Servi S (2010): Impact of acute coronary syndromes on two-year clinical outcomes in patients with unprotected left main coronary artery stenosis treated with drug-eluting stents. Am J Cardiol 105:174-178.

Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M, Xu K, and Stone GW (2011): Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention: Analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial. J Am Coll Cardiol 57:2389-2397.

Park DW, Kim YH, Yun SC, Song HG, Ahn JM, Oh JH, Kim WJ, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, and Park SJ (2011): Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. J Am Coll Cardiol 57:2152-2159.

Parodi O, Uthurralt N, Severi S, Bencivelli W, Michelassi C, L'Abbate A, and Maseri A (1981): Transient reduction of regional myocardial perfusion during angina at rest with ST-segment depression or normalization of negative T waves. Circulation 63:1238-1247.

Perloff JK. (1964): The recognition of strictly posterior myocardial infarction by conventional scaöar electrocardiography. Circulation 30:706-718.

Pitsavos C, Chrysohoou C, Panagiotakos DB, Stefanadis C, and GREECS study investigators (2008): Electrocardiographic findings at presentation, in relation to in-hospital mortality and 30-day outcome of patients with acute coronary syndromes; the GREECS study. Int J Cardiol 123:263-270.

Pitta SR, Grzybowski M, Welch RD, Frederick PD, Wahl R, and Zalenski RJ (2005): ST-segment depression on the initial electrocardiogram in acute myocardial infarction-prognostic significance and its effect on short-term mortality: A report from the national registry of myocardial infarction (NRMI-2, 3, 4). Am J Cardiol 95:843-848.

Polonski L, Gasior M, Gierlotka M, Osadnik T, Kalarus Z, Trusz-Gluza M, Zembala M, Wilczek K, Lekston A, Zdrojewski T, Tendera M, and PL-ACS Registry Pilot Group (2011): A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: Are non-ST myocardial infarctions associated with worse long-term prognoses? Int J Cardiol 152:70-77.

Pope JH, Ruthazer R, Kontos MC, Beshansky JR, Griffith JL, and Selker HP (2004): The impact of electrocardiographic left ventricular hypertrophy and bundle branch block on the triage and outcome of ED patients with a suspected acute coronary syndrome: A multicenter study. Am J Emerg Med 22:156-163.

Porter A, Vaturi M, Adler Y, Sclarovsky S, Strasberg B, Herz I, Kuzniec H, and Birnbaum Y (1998): Are there differences among patients with inferior acute myocardial infarction with ST depression in leads V2 and V3 and positive versus negative T waves in these leads on admission? Cardiology 90:295-298.

Puricel S, Adorjan P, Oberhansli M, Stauffer JC, Moschovitis A, Vogel R, Goy JJ, Muller O, Eeckhout E, Togni M, Wenaweser P, Meier B, Windecker S, and Cook S (2011): Clinical outcomes after PCI for acute coronary syndrome in unprotected left main coronary artery disease: Insights from the Swiss Acute Left main coronary Vessel percutaneous management (SALVage) study. EuroIntervention 7:697-704.

Quigley RL, Milano CA, Smith LR, White WD, Rankin JS, and Glower DD (1993): Prognosis and management of anterolateral myocardial infarction in patients with severe left main disease and cardiogenic shock. The left main shock syndrome. Circulation 88:II65-70.

Raunio H, Rissanen V, Romppanen T, Jokinen Y, Rehnberg S, Helin M, and Pyörälä K (1979): Changes in the QRS complex and ST segment in transmural and subendocardial myocardial infarctions. A clinicopathologic study. Am Heart J 98:176-184.

Reimer KA, Lowe JE, Rasmussen MM, and Jennings RB (1977). The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 56:786-794.

Rentrop KP, Cohen M, Blanke H, and Phillips RA (1985): Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 5:587-592.

Roberts WC, Virmani R (1979): Quantification of coronary arterial narrowing in clinically-isolated unstable angina pectoris. An analysis of 22 necropsy patients. Am J Med 67:792-799.

Ryan JW, Peterson ED, Chen AY, Roe MT, Ohman EM, Cannon CP, Berger PB, Saucedo JF, DeLong ER, Normand SL, Pollack CV, Jr, Cohen DJ, and CRUSADE Investigators (2005): Optimal timing of intervention in non-ST-segment elevation acute coronary syndromes: Insights from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) registry. Circulation 112:3049-3057.

Sakuma H, Suzawa N, Ichikawa Y, Makino K, Hirano T, Kitagawa K, and Takeda K (2005): Diagnostic accuracy of stress first-pass contrast-enhanced myocardial perfusion MRI compared with stress myocardial perfusion scintigraphy. Am J Roentgenol 185:95-102.

Savonitto S, Ardissino D, Granger CB, Morando G, Prando MD, Mafrici A, Cavallini C, Melandri G, Thompson TD, Vahanian A, Ohman EM, Califf RM, Van de Werf F, and Topol EJ (1999): Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 281:707-713.

Savonitto S, Cohen MG, Politi A, Hudson MP, Kong DF, Huang Y, Pieper KS, Mauri F, Wagner GS, Califf RM, Topol EJ, and Granger CB (2005): Extent of ST-segment depression and cardiac events in non-ST-segment elevation acute coronary syndromes. Eur Heart J 26:2106-2113.

Schlesinger MJ (1940): Relation of anatomic pattern to pathologic conditions of the coronary arteries. Arch Path 30:403-415.

Scirica BM, Moliterno DJ, Every NR, Anderson HV, Aguirre FV, Granger CB, Lambrew CT, Rabbani LE, Arnold A, Sapp SK, Booth JE, Ferguson JJ, and Cannon CP (1999): Differences between men and women in the management of unstable angina pectoris (the GUARANTEE registry). The GUARANTEE investigators. Am J Cardiol 84:1145-1150.

Sclarovsky S, Davidson E, Strasberg B, Lewin RF, Arditti A, Wurtzel M, and Agmon J (1986a): Unstable angina: The significance of ST segment elevation or depression in patients without evidence of increased myocardial oxygen demand. Am Heart J 112:463-467.

Sclarovsky S, Davidson E, Lewin RF, Strasberg B, Arditti A, and Agmon J (1986b): Unstable angina pectoris evolving to acute myocardial infarction: Significance of ECG changes during chest pain. Am Heart J 112:459-462.

Sclarovsky S, Rechavia E, Strasberg B, Sagie A, Bassevich R, Kusniec J, Mager A, and Agmon J (1988a): Unstable angina: ST segment depression with positive versus negative T wave deflections--clinical course, ECG evolution, and angiographic correlation. Am Heart J 116:933-941.

Sclarovsky S, Bassevich R, Strasberg, Klainman E, Rechavia E, Sagie A, and Agmon J (1988b): Unstable angina with tachycardia: Clinical and therapeutic implications. Am Heart J 116:1188-1193.

Sclarovsky S. (1999): Angina at rest and acute myocardial ischaemia. In: Electrocardiography of acute myocardial ischaemic syndromes, pp. 1-29. Ed. Sclarovsky S, Martin Dunitz Ltd, London, UK.

Seung KB, Park DW, Kim YH, Lee SW, Lee CW, Hong MK, Park SW, Yun SC, Gwon HC, Jeong MH, Jang Y, Kim HS, Kim PJ, Seong IW, Park HS, Ahn T, Chae IH, Tahk SJ, Chung WS, and Park SJ (2008): Stents versus coronary-artery bypass grafting for left main coronary artery disease. N Engl J Med 358:1781-1792.

Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, van den Brand M, Van Dyck N, Russell ME, Mohr FW, and Serruys PW (2005): The SYNTAX score: An angiographic tool grading the complexity of coronary artery disease. EuroIntervention 1:219-227.

Silvestri M, Barragan P, Sainsous J, Bayet G, Simeoni JB, Roquebert PO, Macaluso G, Bouvier JL, and Comet B (2000): Unprotected left main coronary artery stenting: Immediate and medium-term outcomes of 140 elective procedures. J Am Coll Cardiol 35:1543-1550.

Smith FM. (1918): The ligation of coronary arteries with electrocardiographic study. Arch Intern Med 22:8-27.

Sokolow M, Lyon TP (1949): The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J 37:161-186.

Taglieri N, Marzocchi A, Saia F, Marrozzini C, Palmerini T, Ortolani P, Cinti L, Rosmini S, Vagnarelli F, Alessi L, Villani C, Scaramuzzino G, Gallelli I, Melandri G, Branzi A, and Rapezzi C (2011): Short- and long-term prognostic significance of ST-segment elevation in lead aVR in patients with non-ST-segment elevation acute coronary syndrome. Am J Cardiol 108:21-28.

Takaro T, Hultgren HN, Lipton MJ, and Detre KM (1976): The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. Circulation 54:III107-17.

Teixeira R, Lourenco C, Antonio N, Monteiro S, Baptista R, Jorge E, Ferreira MJ, Monteiro P, Freitas M, and Providencia LA (2010): The importance of a normal ECG in non-ST elevation acute coronary syndromes. Arq Bras Cardiol 94:25-33.

Terkelsen CJ, Lassen JF, Norgaard BL, Gerdes JC, Jensen T, Gotzsche LB, Nielsen TT, and Andersen HR (2005): Mortality rates in patients with ST-elevation vs. non-ST-elevation acute myocardial infarction: Observations from an unselected cohort. Eur Heart J 26:18-26.

Thygesen K, Alpert JS, White HD, and Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction (2007): Universal definition of myocardial infarction. Eur Heart J 28:2525-2538.

Topaz O, Disciascio G, Cowley MJ, Lanter P, Soffer A, Warner M, Nath A, Goudreau E, Halle AA, 3rd, and Vetrovec GW (1991): Complete left main coronary artery occlusion: Angiographic evaluation of collateral vessel patterns and assessment of hemodynamic correlates. Am Heart J 121:450-456.

Topol EJ, GUSTO V Investigators. (2001): Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: The GUSTO V randomised trial. Lancet 357:1905-1914.

Uthamalingam S, Zheng H, Leavitt M, Pomerantsev E, Ahmado I, Gurm GS, and Gewirtz H (2011): Exercise-induced ST-segment elevation in ECG lead aVR is a useful indicator of significant left main or ostial LAD coronary artery stenosis. JACC Cardiovasc Imaging 4:176-186.

Virmani R, Roberts WC (1980): Quantification of coronary arterial narrowing and of left ventricular myocardial scarring in healed myocardial infarction with chronic, eventually fatal, congestive cardiac failure. Am J Med 68:831-838.

Virmani R, Roberts WC (1981): Non-fatal healed transmural myocardial infarction and fatal non-cardiac disease. Qualification and quantification of coronary arterial narrowing and of left ventricular scarring in 18 necropsy patients. Br Heart J 45:434-441.

Virmani R, Robinowitz M, and McAllister HA, Jr (1983): Coronary heart disease in 48 autopsy patients 30 years old and younger. Arch Pathol Lab Med 107:535-540.

Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M, Klocke FJ, Bonow RO, Kim RJ, and Judd RM (2003): Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: An imaging study. Lancet 361:374-379.

Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, and Swahn E (2000): Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: The FRISC II invasive randomised trial. FRISC II investigators. Fast Revascularisation during InSstability in Coronary artery disease. Lancet 356:9-16.

Wasserburger RH, Corliss RJ (1965): Prominent precordial T waves as an expression of coronary insufficiency. Am J Cardiol 16:195-205.

Willems JL, Robles de Medina EO, Bernard R, Coumel P, Fisch C, Krikler D, Mazur NA, Meijler FL, Mogensen L, and Moret P (1985): Criteria for intraventricular conduction disturbances and pre-excitation. World Health Organizational/International Society and Federation for Cardiology task force ad hoc. J Am Coll Cardiol 5:1261-1275.

Yamaji H, Iwasaki K, Kusachi S, Murakami T, Hirami R, Hamamoto H, Hina K, Kita T, Sakakibara N, and Tsuji T (2001): Prediction of acute left main coronary artery obstruction by 12-lead electrocardiography. ST segment elevation in lead aVR with less ST segment elevation in lead V1. J Am Coll Cardiol 38:1348-1354.

Yamane M, Inoue S, Yamane A, Kinebuchi O, and Yokozuka H (2005): Primary stenting for left-main shock syndrome. EuroIntervention 1:198-203.

Yan RT, Yan AT, Granger CB, Lopez-Sendon J, Brieger D, Kennelly B, Budaj A, Steg PG, Georgescu AA, Hassan Q, Goodman SG, and Global Registry of Acute Coronary Events (GRACE) Electrocardiogram Substudy Group (2008): Usefulness of quantitative versus qualitative ST-segment depression for risk stratification of non-ST elevation acute coronary syndromes in contemporary clinical practice. Am J Cardiol 101:919-924.

Zack PM, Aker UT, and Kennedy HL (1987): Pseudonormalization of T-waves during coronary angioplasty. Cathet Cardiovasc Diagn 13:191-193.

Zeymer U, Vogt A, Zahn R, Weber MA, Tebbe U, Gottwik M, Bonzel T, Senges J, Neuhaus KL, and Arbeitsgemeinschaft Leitende Kardiologische Krankenhausarzte (ALKK) (2004): Predictors of in-hospital mortality in 1333 patients with acute myocardial infarction complicated by cardiogenic shock treated with primary percutaneous coronary intervention (PCI); results of the primary PCI registry of the arbeitsgemeinschaft leitende kardiologische krankenhausarzte (ALKK). Eur Heart J 25:322-328.

Zhang XJ, Yan HB, Zheng B, Song L, Wang J, and Chi YP (2010): Reasons for failed electrocardiographic identification of the infarct-related artery in patients with ST-elevation acute myocardial infarction. Zhonghua Xin Xue Guan Bing Za Zhi 38:914-917.

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ST-Depression with Negative T Waves in Leads V_4–V_5—A Marker of Severe Coronary Artery Disease in Non-ST Elevation Acute Coronary Syndrome: A Prospective Study of Angina at Rest, with Troponin, Clinical, Electrocardiographic, and Angiographic Correlation

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Background: The significance of ST-segment depression in acute coronary syndrome has been the subject of debate for many decades. Studies indicate that different manifestations of ST/T changes may have significantly different prognostic implications.

Methods and Results: We studied the correlation of ST/T changes in 12-lead electrocardiography recorded during pain, to clinical and angiographic findings and in-hospital prognosis, in patients with non-ST-elevation acute coronary syndrome and elevated troponin levels. Fifty consecutive patients could be differentiated into two groups: (1) 25 patients with ST-segment depression and a *negative* T wave maximally in leads $V_{4–5}$, (2) 25 patients with ST-segment depression and a *positive* T wave in the precordial lead with maximal ST-segment depression. Patients in group I had significantly more often left main or left main equivalent coronary artery disease; 76% versus 8% ($P < 0.001$), heart failure; 40% versus 4% ($P = 0.005$), and higher in-hospital mortality; 24% versus 0% ($P = 0.02$), than patients in group II. The troponin levels did not differ significantly between the groups.

Conclusions: In patients with non-ST-elevation acute coronary syndrome and elevated troponin levels two subgroups could be identified. Transient ST-segment depression and a *negative* T wave maximally in leads $V_{4–5}$ during anginal pain predicts left main, left main equivalent, or severe three-vessel coronary artery disease with high sensitivity and specificity. In patients with ST-segment depression and a *positive* T wave, there is a high probability of one-vessel disease.

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angina; electrocardiography; prognosis

During the last 60–70 years the significance of ST-segment depression in acute coronary syndrome has been the subject for debate. In 1950, Levine and Ford described cases with subendocardial circumferential myocardial infarction.[1] They correlated anatomic endocardial lesions to electrocardiographic (ECG) changes in six patients with left main or severe three-vessel coronary artery disease (CAD). The ECG changes consisted of widespread ST-segment depression, often associated with widespread inversion of the T wave. These findings have later been confirmed by several authors.[2–5] Cook, Edwards, and Pruitt stated that ST-segment depression and T-wave inversion might occur in transient subendocardial ischemia.[6] They published detailed anatomical studies of large and small subendocardial infarcts, correlating to premortal ECG changes. Despite the studies of

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these legendary groups of investigators, no new progress in the topic appeared during the following years.

The medical communities did not accept the concepts, probably because it was not possible to reproduce circumferential ischemia in the experimental laboratory.

In the mid 1970s a few groups of investigators in Europe started to investigate the mechanisms of rest angina, spontaneous or induced by ergonovine maleate to provoke ischemia.[7,8] They repetitively found that subtotal occlusion of the left anterior descending (LAD) coronary artery, produced ST-segment depression in leads V_{2-4}. The same leads showed ST-segment elevation when the artery was totally occluded.

For some reason, the findings of these two groups have not been compared. The different findings of these groups seem to represent two types of ischemia with significantly different clinical and prognostic differences.

The purpose of our study was to investigate the significance of ST-segment depression and T-wave changes in acute coronary syndrome, with respect to in-hospital prognosis, troponin levels, and angiographic findings, in the modern era of cardiology.

METHODS

Subjects

We studied prospectively and consecutively, from November 2000 to March 2002, patients at Tampere University Hospital with acute coronary syndrome and transient ECG changes. Inclusion criteria were symptoms of myocardial ischemia associated with (1) ST-segment depression (irrespective of orientation of the T wave) or (2) T-wave inversion, in a 12-lead ECG recorded during anginal pain, a positive troponin test, and coronary angiography performed during hospital stay.

Exclusion criteria were ST-segment elevation (apart from leads a VR or V_1), heart rate over 100 beats/min during the ECG recording (as tachycardia induces ST/T changes), structural heart disease, or previous bypass surgery.

We also excluded patients with chronic ECG changes: pathological Q waves, left ventricular hypertrophy, bundle branch block, preexcitation, or pacemakers.

All patients in both groups would have been classified into Braunwald class IIIB based on the clinical manifestation.[9] All of them had rest angina within 48 hours without secondary or postinfarction unstable angina. However, based on the newly introduced criteria, they are classified as non-ST-elevation MI (myocardial infarction).[10]

The study complies with the Declaration of Helsinki. The ethics committee at Tampere University Hospital approved the study protocol. The patients gave their written informed consent for participation.

ECG Analysis

A standard 12-lead ECG with maximal ST-segment depression was chosen for measurements. The ECG was recorded at a paper speed of 50 mm/s at a calibration of 1 mV = 10 mm. Three investigators blinded to the angiographic findings analyzed the ECG manually. If the results were not in accord, consensus was found by discussion among the investigators. ST-segment deviation from the isoelectric line, determined by drawing a line between subsequent PQ segments, was considered elevated or depressed if it was 0.5 mm or more above or below the isoelectric line, respectively. The T wave was considered positive or negative if it was 1 mm or more above or below the isoelectric line, measured more than 120 ms after the J point. The ST-segment and T-wave changes were measured separately from all 12 leads with the aid of a hand held magnifying lens. Left ventricular hypertrophy was defined by the Sokolow–Lyon criteria ($SV_1 + RV_{5-6} \geq 35$ mm). Pathological Q waves were defined by standard criteria.[11]

Laboratory Analysis

Blood samples for troponin I (cTnI) were collected at baseline and after 6–12 hours. The normal value for cTnI in our hospital is <0.2 μg/L (ACS:180, Bayer Diagnostics, Tarrytown, NY).

Echocardiography

All patients underwent echocardiography by the cardiologist performing the coronary angiography. The examination was not done during chest pain. The ejection fraction (EF) was measured. Significant structural heart disease, for example, valve disease, or cardiomyopathy led to exclusion from the study.

Coronary Angiographic Evaluation

Selective coronary angiography by the femoral or radial route was performed in all patients. The indication for angiography was clinical, not investigational, in all cases. In most patients digital x-ray equipment was used. The left coronary artery was evaluated from at least four projections (left and right anterior oblique, anteroposterior cranial, and caudal), and the right coronary artery from at least two projections. A significant stenosis was defined as >50% diameter obstruction of the coronary artery lumen diameter (Fig. 1A). Left main equivalent coronary artery disease (LME-CAD) was defined as a diameter stenosis of >50% in the proximal segment of the left anterior descending and left circumflex artery. Flow in the coronary arteries was graded into four grades (0–3), as described in the Thrombolysis in Myocardial Infarction (TIMI) trial.[12]

Collateral circulation was classed into four grades according to the grading system of Rentrop et al.[13] Briefly, grade 0 was no collateral opacification, grade 1 filling of side branches, grade 2 partial, and grade 3 complete filling of the main branch by collateral vessels.

Severe three-vessel disease (VD) was defined as significant or total obstruction of the proximal or mid-segment of all three main epicardial arteries. Other cases with 3-VD were classified as nonsevere.

The interpreters of the angiography were blinded to the ECG finding.

Statistical Analysis

Proportions were compared with the chi-square test or Fisher's exact test and quantitative data were compared with the Mann–Whitney test. A probability value of <0.05 was considered statistically significant. All calculations were performed with the SPSS 7.5 statistical package.

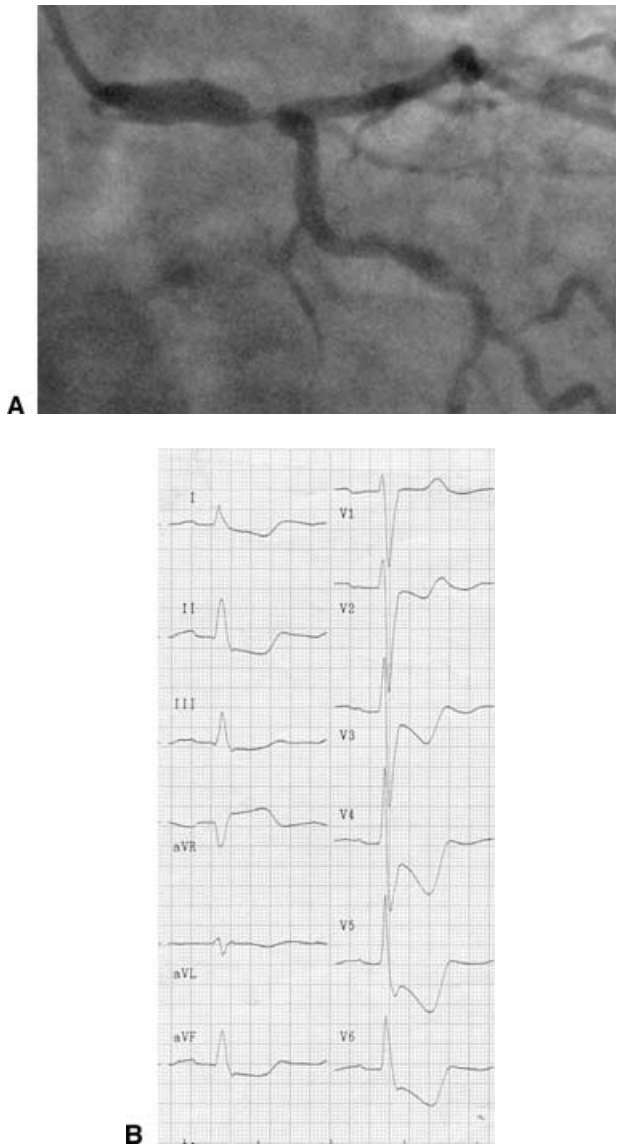


Figure 1. A patient in group I. (A) Coronary angiography shows tight stenosis in the distal left main coronary artery. (B) Electrocardiography (ECG) shows ST-segment depression and inverted T waves, maximally in leads $V_{4–5}$, and ST-segment elevation in lead aVR (circumferential subendocardial ischemia).

RESULTS

We found a total of 52 patients fulfilling the inclusion criteria. Two patients had ST-segment depression in the precordial leads and marginally significant ST-segment elevation in lead III. They were excluded from the study after discussion among the investigators. Accordingly, the study group consisted of 50 patients (30 male, 20 female, mean age 69 ± 10 years). We found no patients with isolated T-wave inversion during rest angina.

Two Patient Groups

According to the results of previous retrospective studies by a study group of one of the authors,[14,15] we decided to divide the patients into two

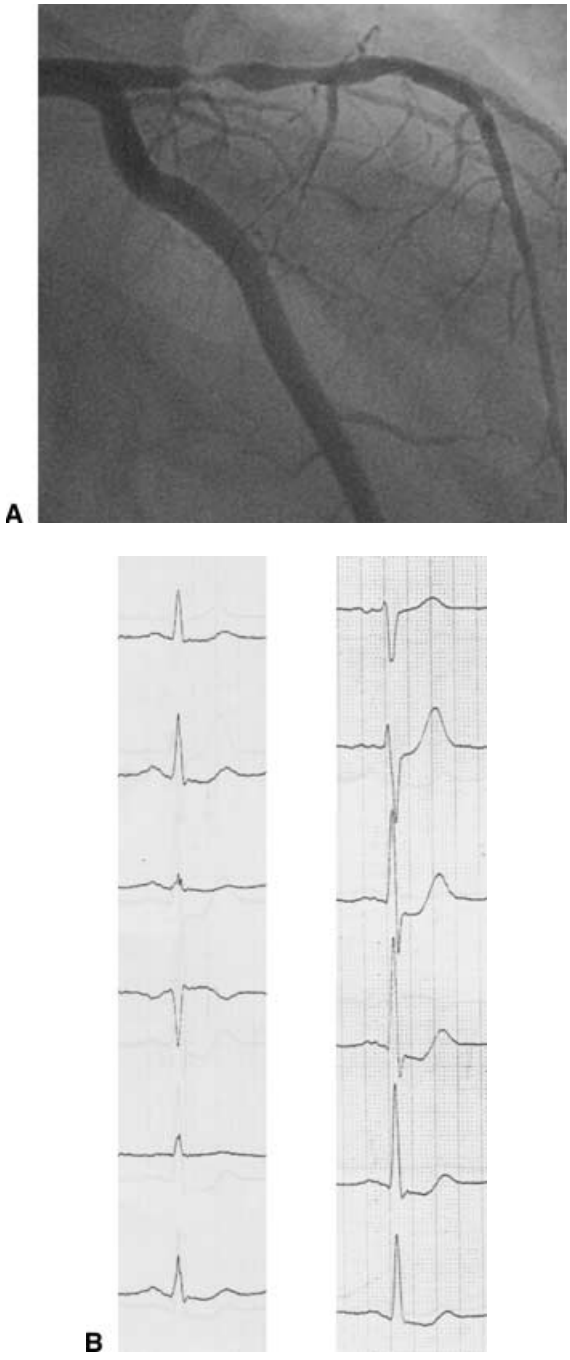


Figure 2. A patient in group II. (A) Angiography shows tight stenosis of the proximal left anterior descending coronary artery. (B) ECG (extremity leads left, precordial leads right) shows ST-segment depression with positive T wave maximally in leads V_{3-5} (regional subendocardial ischemia).

groups: (1) group I (T−) consisted of patients with ST-segment depression and a *negative* T wave maximally in leads V_{4-5} (Fig. 1B), (2) group II (T+) consisted of patients with ST-segment depression and a *positive* T wave in the precordial lead with maximal ST-segment depression (Fig. 2B). By chance the number of patients in both groups was 25. Patients in group I were older than those in group II, were smokers less often, had more often signs of universal atherosclerosis and previous angina pectoris, and were more often on aspirin therapy (Table 1). The cTnI levels were slightly higher in group I (median 11.2 μg/L) than in group II (median 3.1 μg/L), $P = 0.06$. Systolic blood pressure measured during the chest pain episode, when 12-lead ECG was recorded, did not differ between the groups (147 vs 148 mmHg, $P = 0.84$). Diastolic pressure was lower in group I than in group II (73 vs. 81 mmHg, $P = 0.04$).

ECG Findings

Three patients in group I had slow atrial fibrillation. All other patients were in sinus rhythm during the ECG recording. In group I 52% of patients had the maximal ST-segment depression and T-wave inversion in lead V_4 and 48% in lead V_5. All patients in group I also had ST-segment elevation of at least 0.5 mm in lead aVR. In group II all patients had a positive T wave in the lead with maximal ST-segment depression and the localization of the maximal ST-segment depression was in the precordial leads.

Angiographic Findings (Table 2)

The culprit artery could be defined in only 3 of 25 cases in group I. One patient had an acute plaque rupture of the left main coronary artery. In two cases there was significant stenosis in the left main without any other significant stenoses. In group II the culprit artery could be defined in 76% of cases (of these LAD in 74%, left circumflex in 26%). The mean delay from ECG registration to angiography was 7 days in both groups. Collateral flow grade 0 or 1 on angiography was present in 68% in group I and in 92% in group II, and grade 2 or 3 in 32% and 8%, respectively ($P = 0.07$). All patients with transient ST-segment depression and negative T waves, maximally in leads V_{4-5}, had severe 3-VD, LM- or LME-CAD on angiography (Table 3). All patients with severe 3-VD presented with this ECG pattern.

Table 1. Baseline Clinical Characteristics

	Group I (T−) n = 25 (%)	Group II (T+) n = 25 (%)	P Value
Female gender	44	36	0.77
Active smoking	4	32	0.03
Hypertension	60	48	0.57
Diabetes mellitus	20	12	0.70
Universal atherosclerosis	17	0	0.05
Previous angina (>2 months)	68	36	0.05
Previous PCI	0	4	1.00
Previous non-Q MI	21	4	0.19
Previous TIA	25	0	0.01
Renal dysfunction	0	5	0.37
Current use of medication			
Aspirin	68	24	0.004
Beta-blockers	72	48	0.15
Nitrates	60	40	0.26
Calcium-antagonists	32	12	0.17
Digitalis	8	8	1.00
Statins	28	16	0.50
Age years (mean ± SD)	74 ± 6	64 ± 11	0.001

MI = myocardial infarction; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

In-Hospital Follow-up

The in-hospital follow-up event rate was higher in group I than in group II; in-hospital mortality was 24% versus 0%, respectively (Table 4).

DISCUSSION

We set out to prospectively study a well-defined and homogenous group of patients with acute coronary syndrome and ischemic ST-segment depression during pain. We included only patients with transient ECG changes and elevated troponin levels. We excluded patients with confounding factors like left ventricular hypertrophy, bundle branch block, and cardiomyopathy. Based on the localization of the maximal ST-segment depression and the direction of the T wave, we were able to identify two groups of patients, one with severe coronary artery disease and a high in-hospital mortality, and another with predominantly one-vessel disease and a good in-hospital prognosis.

Deviation of the ST segment is a well-recognized sign of ischemia.[16] ST-segment elevation caused by sudden occlusion of a coronary artery is a well-known ECG finding.[17,18] In contrast, transient ST-segment depression in the precordial leads may be caused by different mechanisms like tachycardia,[19] remodeling in chronic Q-wave anterior MI,[20] inferoposterior MI (reciprocal phenomenon[21] or a sign of multivessel CAD[22]), and regional ischemia.[8]

In 1946 Bayley described the correlation between subendocardial MI and ST-segment depression.[23] This ECG finding, typical of diffuse

Table 2. Coronary Angiography Findings

Number of Diseased Vessel	Group I (T−) n = 25 (%)	Group II (T+) n = 25 (%)	P Value
0-VD	0	8	0.49
1-VD	0	56	<0.001
2-VD	0	8	0.49
Nonsevere 3-VD	0	20	0.05
Severe 3-VD	24	0	0.02
LM-CAD or LME-CAD	76	8	<0.001

LM-CAD = left main coronary artery disease; LME-CAD = left main equivalent coronary artery disease; VD = vessel disease.

Table 3. The Sensitivity, Specificity , Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for the ECG Pattern with Transient ST-Segment Depression and Negative T Waves During Pain, Maximally in Leads V_{4-5}, to Predict Different Coronary Artery Disease Severity in Angiography

Angiography Findings	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Severe 3-VD	100	57	24	100
LM- or LME-CAD	91	79	76	92
Severe 3-VD or LM- or LME-CAD	93	100	100	92

Abbreviations as in Table 2.

injury of the subendocardial layer, was described as "injury-against-the-rule," that is, ST depression recorded by a precordial lead with the exploring electrode superjacent to an injured region.[24] In the 1940s researchers searched for the electrocardiographic manifestation of subendocardial injury.[25,26] It proved difficult, if not impossible, to produce subendocardial damage of sufficient extent and severity to produce measurable electrical effects while sparing a zone of uninjured myocardium between the traumatized tissue and the epicardium in animal models. Levine stated: "Nature, it seems, can fulfill the conditions of this experiment much more readily than can the physiologist."[1] Still, in the modern era of cardiology, the prognostic implications of different ECG presentations of acute myocardial ischemia without ST-segment elevation have not been well defined.[27]

The Importance of ST-Segment Depression and Inverted Asymmetric T Waves in Patients without Tachycardia (group I)

We found that the ECG pattern of ST-segment depression and inverted T waves, maximally in leads V_{4-5}, was strongly associated with LM-CAD, LME-CAD, or severe 3-VD. This ECG pattern has been described by one of the authors as acute circumferential subendocardial ischemia.[28] Forty percent of the patients had clinical signs of heart failure, mostly pulmonary edema. The in-hospital mortality was high.

Extensive ischemia, for example, caused by sudden obstruction of the left main coronary artery, impairs the relaxation of the left ventricle.[29] The resulting increase in left ventricular end-diastolic pressure induces severe subendocardial ischemia. Elevation of left ventricular preload explains the high frequency of pulmonary edema in these cases. In animals a constriction of the left main coronary artery, causing global left ventricular ischemia, resulted in a significant decrease in the endocardial-to-epicardial flow ratio and a significant increase of end-diastolic left ventricular transmural pressure.[30]

Acute circumferential subendocardial MI is a well-known clinical, electrocardiographic, and pathologic entity. Many authors have described the pattern of ST-segment depression, often with negative T waves, as the typical ECG finding in these patients.[2–5] ST-segment elevation in leads aVR and V_1, reflects cavity potentials from the left ventricle, directed toward the right shoulder, consistent with injury of the subendocardial layer.[5]

Table 4. In-Hospital Follow-Up

	Group I (T−) n = 25 (%)	Group II (T+) n = 25 (%)	P-value
Clinical signs of heart failure	40	4	0.005
Ejection fraction			
30–49%	42	8	0.008
≥50%	58	92	0.008
CABG	76	20	<0.001
PCI	12	52	0.005
In-hospital mortality	24	0	0.02

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

ST-Segment Depression with Positive T Wave (group II)

Coronary angiography findings in the patients in group II were significantly less severe than those of the patients in group I. The majority of patients in group II had 1-VD, about three quarters of these in LAD (Fig. 2A). Fifty-two percent were treated by coronary angioplasty, and 20% by bypass surgery. In contrast only 12% in group I had angioplasty, and 76% bypass surgery. Only 1 patient in group II had clinical signs of heart failure, and the EF was normal in 92% of patients.

Repolarization of the ventricles generates the T wave. The cellular bases for the repolarization waves in the ECG are not well known. Animal studies have shown that the morphology of the T wave measured across the left ventricular wall appears to be due in large parts to currents flowing down voltage gradient present on the epicardial and endocardial sides of the M-cell layer, during phases 2 and 3 of the ventricular action potential.[31] Whether the transmural repolarization gradients suggested by in vitro studies are manifest in humans has been the subject of ongoing controversy.[32] In dogs coronary artery ligation resulted in shortening of the action potential in the ischemic epicardial layer generating a tall and peaked T wave.[33] The first electrocardiographic manifestation of a subtotal obstruction of LAD in one-vessel disease is ST-segment depression and a positive T wave.[8] The tall T waves are probably caused by high extracellular potassium.[34] This is related to a hyperpolarization of the myocytes due to an opening of the K^+-ATP channel.[35] ST-segment depression in these patients is most probably caused by a regional, nonextensive, subendocardial ischemia.[7,8,28] Our finding that no patients in group II had pulmonary edema, and that there was no severe 3-VD supports this finding. ST-segment depression with positive T wave has been associated with a high incidence of 1-VD.[14] The dissociation between ST-segment and T-wave orientation is an unusual ECG finding, and represents a challenge for ECG interpretation in acute ischemic syndromes.

Limitations

The number of patients is small. We think, though, that the message from this study has great clinical impact. We did not include patients with normal troponin levels or ST-segment elevation (apart from leads aVR or V_1). There may be some patients with LM- or LME-CAD presenting with this ECG pattern.

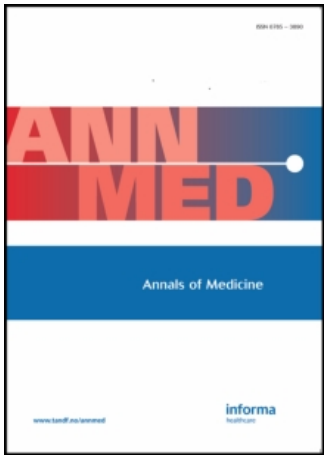
Clinical Implications

Our task was to try to prospectively test the relevance of the findings in the literature that different types of ST-segment depression and T wave changes represent different types of ischemia. Despite the small number of patients the results showed a highly significant statistical difference in disease severity between two groups of patients with distinct prespecified ST/T changes. Our finding should have important clinical impact.

REFERENCES

1. Levine HD, Ford RV. Subendocardial infarction: Report of six cases and critical survey of the literature. Circulation 1950;1:246–263.
2. Myers GB, Sears CH, Hiratzka T. Correlation of electrocardiographic and pathologic findings in ring-like subendocardial infarction of the left ventricle. Am J Med Sci 1951;222:417–426.
3. Hackel DB, Wagner GS. Acute circumferential subendocardial infarction. Clin Cardiol 1992;15:373–376.
4. Raunio H, Rissanen V, Romppanen T, et al. Changes in the QRS complex and ST segment in transmural and subendocardial myocardial infarctions. A clinicopathological study. Am Heart J 1979;98:176–184.
5. Yu PNG, Stewart JM. Subendocardial myocardial infarction with special reference to the electrocardiographic changes. Am Heart J 1950;39:862–880.
6. Cook RW, Edwards JE, Pruitt RD. Electrocardiographic changes in acute subendocardial infarction. I. Large subendocardial and large nontransmural infarcts. Circulation 1958;18:603–612.
7. De Servi S, Spechia G, Angoli L. Coronary artery spasm of different degrees as cause of angina at rest with ST segment depression and elevation. Br Heart J 1979;42:110–112.
8. Parodi O, Uthurralt N, Severi S, et al. Transient reduction of regional myocardial perfusion during angina at rest with ST-segment depression or normalization of negative T waves. Circulation 1981;63:1238–1247.
9. Braunwald E. Unstable angina: A classification. Circulation 1989;80:410–414.
10. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of the Joint European Society/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. Eur Heart J 2000;21:1502–1513.
11. ACC Clinical data Standards. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndrome. J Am Coll Cardiol 2001;38:2114–2130.
12. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142–154.

13. Rentrop KP, Cohen M, Blanke H, et al. Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. J Am Coll Cardiol 1985;5:587–592.
14. Sclarovsky S, Rechavia E, Strasberg B, et al. Unstable angina: ST segment depression with positive versus negative T wave deflections—clinical course, ECG evolution, and angiographic correlation. Am Heart J 1988;116:933–941.
15. Sclarovsky S, Davidson E, Strasberg B, et al. Unstable angina: The significance of ST segment elevation or depression in patients without evidence of increased myocardial oxygen demand. Am Heart J 1986;112:463–467.
16. Mirvis DV, Goldberger AL. Electrocardiography. In Braunwald E, Zipes DP, Libby P (eds.): Heart Disease. Philadelphia, PA, W.B. Saunders, 2001, pp. 82–128.
17. Wilson FN, Johnston FD, Hill IGW, et al. The electrocardiogram in later stages of experimental myocardial infarction. Proc Assoc Am Physicians 1933;48:154–163.
18. Pardee HEB. An electrocardiographic sign of coronary artery obstruction. Arch Intern Med 1920;26:244–257.
19. Serizawa T, Carabello B, Grossman W. Effect of pacing inducing ischemia on left ventricular diastolic pressure-volume relations in dogs with coronary stenoses. Circ Res 1980;46:430–439.
20. Assali A, Sclarovsky S, Herz I, et al. The clinical significance of ST-segment depression with inverted T wave in V4-V6 in chronic anterior myocardial infarction. J Am Coll Cardiol 2000;35:352–357.
21. Sclarovsky Y, Topaz O, Rechavia E. Ischemic ST segment depression in leads V2-V3 as the presenting electrocardiographic feature of posterolateral wall myocardial infarction. Am Heart J 1987;113:1085–1090.
22. Hasdai D, Sclarovsky S, Solodky A, et al. Prognostic significance of maximal precordial ST-segment depression in right (V1 to V3) versus left (V4 to V6) leads in patients with inferior wall acute myocardial infarction. Am J Cardiol 1994;74:1081–1084.
23. Bayley RH. The electrocardiographic effects of injury at the endocardial surface of the left ventricle. Am Heart J 1946;31:677–684.
24. Bayley RH, LaDue JS. The electrocardiographic evidence of local ventricular ischemia. Symposium on heart disease sponsored by Louisiana State University. Baton Rouge, LA, Louisiana State University Press, 1944.
25. Wolferth CC, Bellet S, Livezey MM, et al. Negative displacement of ST segment in the electrocardiogram and its relationship to positive displacement. An experimental study. Am Heart J 1945;29:220–245.
26. Sodi-Pallares D, Vizcaino M, Soberon J, et al. Comparative study of the intracavitary potential in man and dog. Am Heart J 1947;33:819–848.
27. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999;281:707–713.
28. Sclarovsky S. Electrocardiography of Acute Myocardial Ischaemic Syndromes. London, UK, Martin Dunitz Ltd, 1999, p. 15.
29. Baim DS, Grossman W. Grossman's Cardiac Catheterization, Angiography, and Intervention. 6th edition. Philadelphia, PA, Lippincott Williams & Wilkins, 2001, p. 382.
30. Visner MS, Arentzen CE, Parrish DG, et al. Effects of global ischemia on the diastolic properties of the left ventricle in the conscious dog. Circulation 1985;71:610–619.
31. Yan G-X, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation 1998;98:1928–1936.
32. Antzelevitch C. Transmural dispersion of repolarization and the T wave. Cardiovasc Res 2001;50:426–431.
33. Burgess MJ, Lux RL. Physiologic basis of the T wave. In Schlant RS, Hurst JW (eds.): Advances in Electrocardiography. Vol 2. New York, NY, Grune & Stratton, 1976, pp. 327–337.
34. Katz AM. Physiology of the Heart. 3rd ed. Philadelphia, PA, Lippincott Williams & Wilkins, 2001, p. 644.
35. Kondo T, Kubota I, Tachibana H, et al. Glibenclamide attenuates peaked T wave in early phase of myocardial ischemia. Cardiovasc Res 1996;31:683–687.



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ORIGINAL ARTICLE

Mortality of patients with acute coronary syndromes still remains high: A follow-up study of 1188 consecutive patients admitted to a university hospital

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Abstract

Background. Based on randomized clinical trials, mortality of acute coronary syndrome (ACS) has been considered to be relatively low. The prognosis of clinical presentations of ACS in real-life patient cohorts has not been well documented.

Aim. The aim of this study was to evaluate actual clinical outcome across the whole spectrum of ACS in a series of unselected prospectively collected consecutive patients from a defined geographical region, all admitted to one university hospital.

Methods. A total of 1188 patients with ST-elevation myocardial infarction (STEMI), non-ST-elevation MI (NSTEMI) or unstable angina pectoris (UA) were included.

Results. In-hospital mortality was 9.6%, 13% and 2.6% ($P<0.001$) and mortality at a median follow-up of 10 months 19%, 27% and 12% ($P<0.001$), for the three ACS categories, respectively. In multivariate Cox regression analysis age, diabetes mellitus type 1, diuretic use at admission, creatinine level, lower systolic blood pressure, STEMI and NSTEMI ACS category were associated with higher mortality during follow-up.

Conclusions. In an unselected patient cohort, short-term mortality of MI patients, especially those classified as NSTEMI, still was high despite increasing use of proven treatment modalities.

Key words: *Acute coronary syndrome, myocardial infarction, prognosis, unstable angina*

Introduction

Acute coronary syndrome (ACS) is categorized, according to the clinical picture, presenting electrocardiogram (ECG) and laboratory tests for myocardial necrosis, into ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI) or unstable angina pectoris (UA). In Finland, coronary heart disease mortality declined steeply during the 10-year period of the FINMONICA project 1983–1992, suggesting a change in the clinical picture of coronary events to a less definite and milder direction (1).

Data on mortality in prospectively collected patients from all three categories of ACS are sparse. There seems to be a discrepancy in reported mortality of ACS patients between prospective randomized clinical studies and unselected cohorts (2,3). Mortality of real-life patients is higher. For example, a population-based MI register, the FINAMI study, has shown a 28-day case fatality of 11.5% in men and 9.5% in women in hospitalized patients (4). Strict inclusion and exclusion criteria in randomized trials could explain some of the differences in outcome compared to unselected cohort studies.

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Abbreviations

ACS	acute coronary syndrome
ECG	electrocardiogram
STEMI	ST-elevation myocardial infarction
NSTEMI	non-ST-elevation myocardial infarction
UA	unstable angina pectoris
MI	myocardial infarction
cTnI	cardiac troponin I
LBBB	left bundle branch block
CRP	C-reactive protein
PCI	percutaneous coronary intervention
CABG	coronary artery bypass grafting

The purpose of this study was to evaluate the prognosis of the three different clinical entities of ACS in prospectively collected consecutive patients admitted to a university hospital.

Material and methods

Study population

The TACOS (Tampere Acute COronary Syndrome) study enrollment region encompassed the city of Tampere and 11 neighboring municipalities, in all 340,000 inhabitants. In this region practically all patients with ACS are admitted to Tampere University Hospital. Patients were collected by a study nurse and two of the investigators. During a study period from 1 January 2002 to 31 March 2003 we recruited all patients admitted to the emergency department of our hospital presenting with acute myocardial infarction (MI) as verified by elevated blood troponin (cTnI >0.2 μg/L) value. In addition, from 1 September 2002 to 31 March 2003 we also recruited all consecutive troponin-negative patients with UA. Patients initially treated for ACS in other hospitals or those transferred from another department within our hospital were not included. Patients who died in or were discharged from the emergency department were not included. The final study population, from which all statistical analyses were performed, consisted of 1188 patients, 343 with STEMI, 655 with NSTEMI and 190 with UA. From 1 September 2002 to 31 March 2003, the period when all three ACS categories were included, the following relative proportion of patients ($n=588$) was observed: 143 with STEMI (25%), 255 with NSTEMI (43%) and 190 with UA (32%).

The study complies with the Declaration of Helsinki. The ethics committee at Tampere University Hospital approved the study protocol. The patients gave their written informed consent for participation.

Key message

- In an unselected patient cohort, both in-hospital and mid-term mortality of MI patients, especially those classified as NSTEMI, was considerably higher than expected from clinical trials or voluntary-based cohorts.

ECG analysis

An ECG recorded either in the emergency department, in the ambulance or at the referring health center with maximal ischemic changes was chosen for analysis. Two of the investigators (KCN and MJE) analyzed the ECGs manually with the aid of a hand-held magnifying lens. If the results were not in accordance, consensus was found by discussion between the investigators. ST-segment deviation from the isoelectric line, determined by drawing a line between subsequent PQ segments, was considered elevated or depressed if it was 0.5 mm or more above or below the isoelectric line, respectively. Pathological Q waves were defined as follows: 1) in leads $V_{1\text{-}3}$ any Q wave $\geqslant$30 msec in duration; 2) in leads I, II, aVL, aVF, $V_{4\text{-}6}$ Q wave $\geqslant$1 mm in height and $\geqslant$30 msec in duration in $\geqslant$2 adjacent leads; and 3) in leads $V_{1\text{-}2}$ R wave duration >40 msec and R/S ratio >1 in the absence of pre-excitation, right ventricular hypertrophy or right bundle branch block.

The type of MI was categorized based on the presenting ECGs. STEMI was present if ST-segment elevation was present in two adjacent leads: in leads $V_{1\text{-}6}$ $\geqslant$1.5 mm with $\geqslant$2 mm in at least one lead, in leads II, III, aVF, I and aVL $\geqslant$1 mm.

Troponin

Blood samples for troponin I (cTnI) were collected at baseline and after 6–12 hours. The normal value for cTnI in our hospital is <0.2 μg/L (ACS:180, Bayer Diagnostics, Tarrytown, New York). The maximal value from those two samples was chosen for statistical analysis.

ACS categories

All patients were admitted for symptoms and/or clinical signs suggestive of an ACS. Patients with STEMI had elevated cTnI levels and fulfilled the

above-mentioned ECG criteria. Patients with NSTEMI had elevated cTnI levels and clinical features of ACS, but did not fulfill ECG criteria for STEMI. Patients with left bundle branch block (LBBB) were categorized as having either NSTEMI ($n=60$) or UA ($n=11$) according to the troponin levels. Seven of these (9%) were treated by thrombolytic therapy. UA patients showed no elevation in a minimum of two cTnI levels 6–12 hours apart, and the ECG changes were not predefined.

Data collection

The following information was registered: baseline demographic variables, medication at hospital admission, Canadian Cardiovascular Society and New York Heart Association functional class before the acute phase, plasma creatinine, C-reactive protein (CRP) (twice with a 6–12-h interval), blood lipids, blood pressure at admission, type of reperfusion therapy, in-hospital events (UA, stroke, reinfarction, resuscitation and death), medication during hospital stay, ejection fraction by echocardiography, angiography, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during hospital stay. In coronary angiography $>50\%$ stenoses were considered significant.

A study nurse contacted all patients alive by telephone to collect follow-up data. Follow-up was closed in February 2005. Causes of death were registered from official statistics. Patient follow-up ended in case of death from any cause or at the time of the phone call by the study nurse. Median follow-up was 302 days (inter-quartile range (IQR) 239–331 days), 298 days (IQR 233–321 days) and 439 days (IQR 421–455 days) for STEMI, NSTEMI and UA categories, respectively. Two patients were lost from follow-up.

Statistical analysis

Categorical variables were expressed as numbers of patients or percent, and continuous variables as medians (IQR). Proportions were compared with the chi-square test or Fisher's exact test, and quantitative data were compared with the Mann-Whitney or the Kruskal-Wallis test. A probability value of <0.05 was considered statistically significant. Unadjusted survival data were plotted as Kaplan-Meier curves. Comparison between groups was performed using log rank statistics. Cox regression was used to test the prognostic significance of baseline and in-hospital variables concerning mortality at follow-up. The following variables were not considered for inclusion in the multivariate model because of lack of data for a significant proportion of patients: blood lipids, coronary angiographic findings and ejection fraction. Hazard ratios were presented. Variables with $P<0.20$ in the Cox univariate analysis were included in the multivariate Cox regression model. A stepwise backward elimination method was used to perform variable selection in the multivariate Cox regression analysis each time excluding the one variable with the highest P-value. Variables with $P<0.05$ were included in the final model. All calculations were performed with the SPSS 12.0 statistical package.

Results

Baseline characteristics and in-hospital data are presented in Table I. The median age of the whole study population ($n=1188$) was 73 years (63–80 years). Duration of hospital stay was 7 days (IQR 5–11 days) for the whole study population; 8 days (IQR 6–11 days), 8 days (IQR 5–12 days) and 5 days (IQR 4–8 days) for the STEMI, NSTEMI and UA categories, respectively ($P<0.001$). Unadjusted in-hospital crude mortality in the whole study cohort was 10.4%. Mortality increased to 23% during a median follow-up of 10 months. In-hospital mortality for STEMI, NSTEMI and UA categories was 9.6% ($n=33$), 13% ($n=85$) and 2.6% ($n=5$) ($P<0.001$), respectively (Figure 1). The corresponding numbers for the whole follow-up period was 19% ($n=66$), 27% ($n=179$) and 12% ($n=22$), respectively ($P<0.001$) (Figure 2). There was no difference in unadjusted mortality during the whole follow-up period between STEMI patients who were treated with thrombolytic therapy (18%) compared to those not receiving a thrombolytic agent (21%) (log rank test, $P=0.57$). The mortality increase in the UA category from 2.6% to 12% was due to 17 additional deaths after one year. Of these, six patients died of acute myocardial infarction, two of congestive heart failure, two of stroke, three of non-cardiovascular causes and four of causes unknown to the investigators.

Variables predicting mortality at follow-up according to Cox univariate regression analyses are presented in Table II. In the whole study cohort CRP at admission was associated with mortality, while cTnI level was not.

In multivariate analysis the following variables were independently associated with mortality: age, diabetes mellitus type 1, diuretic use at admission, creatinine level, low systolic blood pressure on admission, PCI procedure, STEMI and NSTEMI ACS category (Table III).

Table I. Baseline characteristics and in-hospital data according to different categories of acute coronary syndrome (n=1188).

	STEMI % (n=343)	NSTEMI % (n=655)	UA % (n=190)	P-value
Age, median (IQR)	69 (59–77)	75 (68–81)	68 (56–76)	<0.001
Female gender	36	46	37	0.003
Active smoking	24	15	15	<0.001
Ex-smoker	44	43	56	0.015
Hypertension	52	55	50	0.297
Diabetes mellitus	22	29	22	0.065
Prior angina (>3 months)	38	53	78	<0.001
Prior PCI or CABG	3	6	17	<0.001
Previous MI	19	27	25	<0.001
Plasma creatinine [a] (μmol/L)	84	91	80	<0.001
C-reactive protein [a] (mg/L)	15.4	17	2.7	<0.001
cTnI [a] (μg/L)	32.4	4.5	–	<0.001
CCS class				<0.001
1–2	28	34	51	
3–4	5	11	26	
Medication at admission				
Aspirin	35	46	57	<0.001
Beta-blocker	40	51	61	<0.001
Nitrate	29	54	61	<0.001
Calcium-antagonist	18	22	22	0.406
Diuretic	19	42	32	<0.001
Statin	16	21	38	<0.001
ACE- or AT2-inhibitor	16	25	21	<0.004
Warfarin	7	14	16	0.006
Clopidogrel	0.6	0.8	2.6	0.086
GP-inhibitor in hospital	33	26	5	<0.001
Medication at discharge				
Aspirin	95	86	82	<0.001
Beta-blocker	97	93	85	<0.001
Nitrate	73	75	64	0.018
Calcium-antagonist	9	21	25	<0.001
Diuretic	51	70	44	<0.001
Statin	71	51	53	<0.001
ACE- or AT2-inhibitor	61	52	40	<0.001
Warfarin	27	24	22	0.292
Clopidogrel	30	19	5	<0.001
EF median (IQR), n=557	52 (40–70)	55 (41–70)	55 (45–65)	0.655
CAG data available	48	41	19	<0.001
Number of diseased vessels				<0.001
<50% stenosis	5	12	28	
1-vessel disease	37	26	36	
2-vessel disease	34	24	14	
3-vessel disease	24	38	22	
Left main disease [b]	5	11	6	0.073
PCI in hospital	24	13	4	<0.001
CABG in hospital	9	11	7	0.244

STEMI=ST-elevation myocardial infarction; NSTEMI=non-ST-elevation myocardial infarction; UA=unstable angina; IQR=Interquartile range; PCI=percutaneous coronary intervention; CABG=coronary artery bypass surgery; MI=myocardial infarction; cTnI=cardiac troponin I; CCS=Canadian Cardiovascular Society; ACE=angiotensin-converting enzyme; AT2=angiotensin II; GP=glycoprotein IIb/IIIa; EF=ejection fraction; CAG=coronary angiography. [a] Values at admission, for cTnI and C-reactive protein: highest of two values 6–12 h apart. [b] Either isolated or in association with 1-, 2- or 3-vessel disease.

Discussion

The present study is unique in evaluating unselected patients with different clinical manifestations of ACS. Our results show that the majority of patients (75%) had a hospital admission diagnosis of non-ST-elevation ACS. Compared to randomized trials, 'real-life' ACS patients are much older (mean age over 70 years), and they appear to have markedly higher mortality both in-hospital and during later follow-up.

Mortality

In recently published randomized trials, in-hospital mortality of STEMI patients has been close to 5%

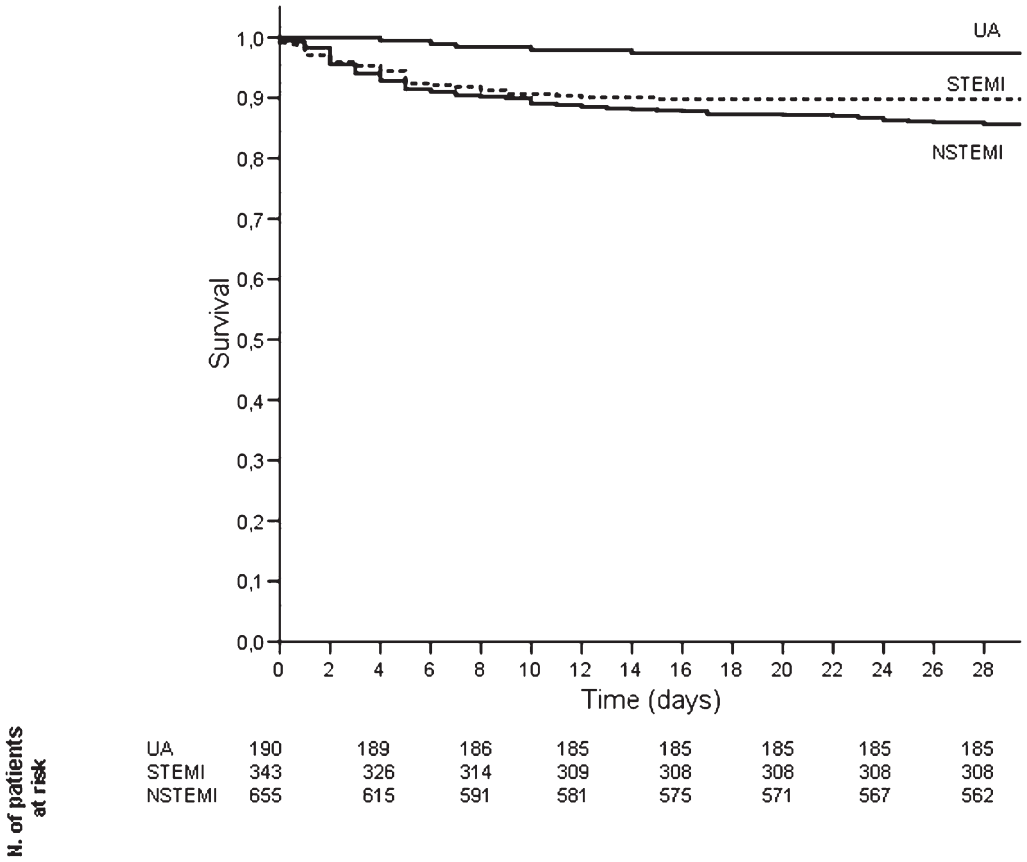

Figure 1. Kaplan-Meier estimates of 28-day survival in the three acute coronary syndrome categories (STEMI=ST-elevation myocardial infarction; NSTEMI=non-ST-elevation myocardial infarction; UA=unstable angina pectoris).

(5,6). In our patients, including all-comers, in-hospital mortality was 9.6%. The mortality of cardiogenic shock, representing about 6%–8% of STEMI patients, is still in the range of 50%–70% despite improvements in reperfusion therapy (7). Shock patients are usually excluded from randomized STEMI studies. In a study by Jha et al. there was significantly higher (>16% versus <7%) in-hospital mortality for non-participants compared to participants in clinical trials (8). In the GRACE registry reporting in-hospital mortality of 5%, patients dying within 24 hours of admission tended to be excluded (9). The FINAMI study, a population-based MI registration conducted during 1983–1997, showed the most marked decline in coronary heart disease mortality outside hospital. There was also a modest reduction in the 28-day case fatality. In 1993–1997 the 28-day case fatality for hospitalized patients was 11.5% in men and 9.5% in women (4). Although STEMIs and NSTEMIs were not considered separately in FINAMI, and criteria for MI were not strictly comparable with those used in the present study, the results of these two studies are rather similar.

A meta-analysis of 23 randomized trials comparing primary PCI with thrombolytic therapy showed long-term mortality (6–18 months) close to 10% in both groups (10). These numbers are certainly lower than those of 'real-life' materials. Björklund et al. found a vastly different 1-year mortality of STEMI trial participants versus non-participants, of 8.8% versus 20.3%, in the Swedish Register of Cardiac Intensive Care (11). 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 fits in with the 20.5% 1-year mortality of STEMI patients reported by Terkelsen et al. and the 19.2% at a mean follow-up of 10 months in our study (12). The study by Björklund et al. also showed, in accordance with previous trials, that patients of lower age, male sex and with fewer risk factors of poor outcome were more likely to be included in trials with thrombolytic agents. Our study shows that when studying all-comers, one patient in five with STEMI will have a fatal event within one year of hospital admission. Efforts are needed to improve these high mortality figures by optimizing early risk stratification and

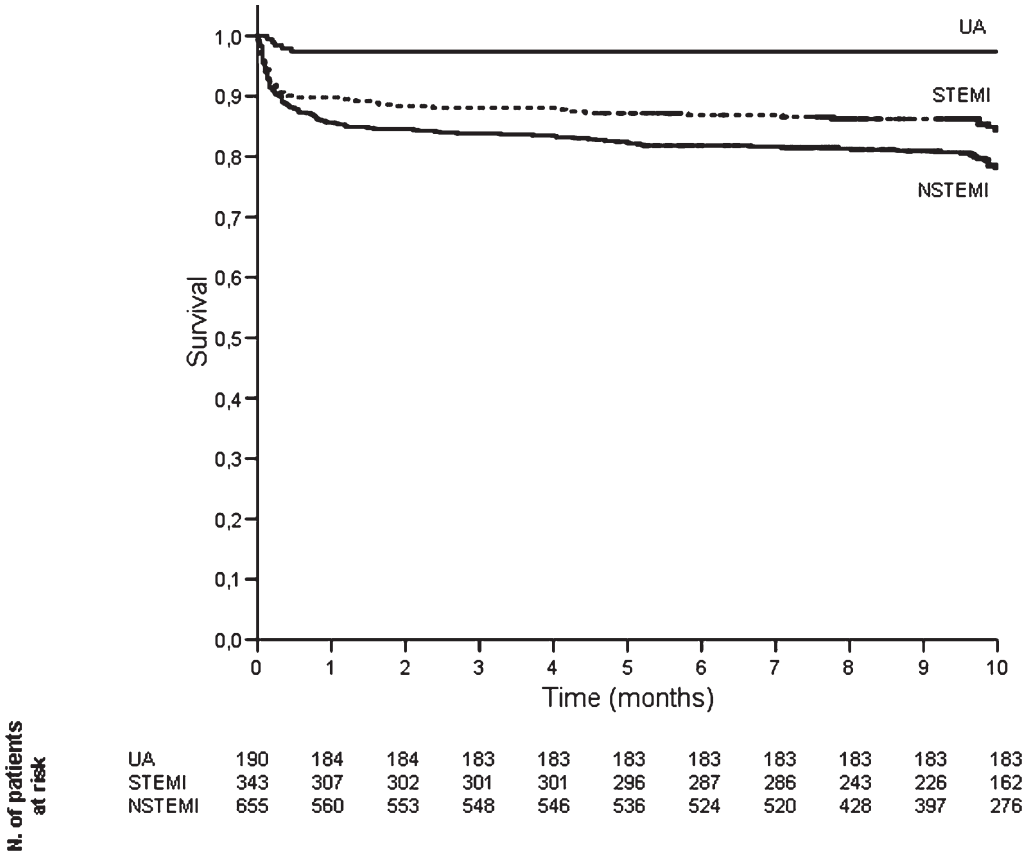

Figure 2. Kaplan-Meier estimates of survival during 10-month follow-up in the three acute coronary syndrome categories (STEMI=ST-elevation myocardial infarction; NSTEMI=non-ST-elevation myocardial infarction; UA=unstable angina pectoris).

implementation of evidence-based medical and invasive therapy.

We found that, in addition to high in-hospital mortality (13%), NSTEMI patients continued to have fatal events, ending up with a very high (27%) mortality at a mean follow-up of 10 months. Mortality was actually higher for NSTEMI than STEMI patients both in hospital and for the whole follow-up period. As previous studies have shown, the vast majority of events in NSTEMI and STEMI patients occur in the first few days or weeks after the initial attack (13,14). Previous studies have indicated that the higher unadjusted mortality of patients with NSTEMI, compared to other ACS patients, could be explained by more pronounced comorbidity (15). In the present study, however, NSTEMI ACS category retained its significance as an independent negative prognostic factor in multivariate Cox regression analyses. This could, at least in part, be explained by the observed more severe coronary artery disease. As less than half of our patients had coronary angiography during the hospital stay, we could not include angiographic disease severity in the multivariate model.

High mortality observed in recent real-life studies might in part be explained by redefinition of diagnostic criteria for ACS. In fact, patients being diagnosed as having MI by the new criteria using troponins appear to be at high risk of dying or having a reinfarction (16). In the National Registry of Myocardial Infarction 4 observational study, treatment deficiencies probably contributed to the high in-hospital mortality rates observed in the STEMI (14.3%) and NSTEMI (12.5%) populations (17).

In-hospital mortality of patients with UA in our study was only 2.6%. No additional deaths appeared up to 6 months. The 28-day mortality of 2681 patients with unstable angina in five Spanish registries, 2.2% in men (mean age 63.6 years) and 3.5% in women (mean age 68.6 years), was in the same range as in our study (18). In our study mortality in UA patients during the whole follow-up period increased, but this could be only a chance phenomenon due to the small number of patients.

Predictors of mortality

This study confirms the prognostic importance of several baseline characteristics reported by other

Table II. Prognostic significance of selected variables concerning mortality at follow-up (median 10 months) according to univariate Cox regression analyses.

	Median (IQR) or %	Valid cases	*P*-value	Hazard ratio	95% CI
Age	73 (63–80)	1188	<0.001	1.072	1.058–1.086
Female gender	42	1188	0.002	1.458	1.147–1.855
Active smoking	19	1081	0.594	0.903	0.621–1.314
Ex-smoker	45	849	0.503	0.893	0.642–1.243
Hypertension	54	1184	0.438	1.102	0.862–1.409
Prior angina (>3 months)	46	1045	0.992	0.998	0.740–1.348
Diabetes					
No diabetes	74	1184		1	
Diabetes mellitus type 1	1	1184	0.233	1.828	0.678–4.928
Diabetes mellitus type 2	25	1184	<0.001	1.720	1.332–2.221
Previous MI	24	1172	0.014	1.388	1.068–1.804
Plasma creatinine (μmol/L)	85 (71–106)	1187	<0.001	1.005	1.004–1.006
cTnI (μg/L)	4.7 (0.6–26)	1188	0.329	1.000	1.000–1.001
C-reactive protein (mg/L)	4.1 (1.5–16)	1170	<0.001	1.005	1.003–1.007
Systolic blood pressure	145 (126–166)	1187	<0.001	0.988	0.984–0.993
Diastolic blood pressure	80 (69–91)	1187	<0.001	0.984	0.977–0.991
Medication at admission					
Aspirin	45	1184	0.131	1.205	0.946–1.534
Beta-blocker	50	1186	0.790	1.033	0.812–1.315
Diuretic	34	1186	<0.001	2.798	2.194–3.567
Statin	22	1187	<0.001	0.511	0.363–0.718
ACE-inhibitor	22	1185	0.026	1.361	1.038–1.785
Thrombolytic therapy (STEMI)	57	343	0.558	0.864	0.530–1.409
PCI [a]	15	1188	<0.001	0.424	0.266–0.677
CABG	9	1188	0.016	0.490	0.275–0.875
Category of ACS		1188			
UA	16			1	
STEMI	29		<0.001	3.405	2.038–5.688
NSTEMI	55		<0.001	5.736	3.542–9.289
CAG data available		470			
<50% stenosis	11			1	
1-vessel disease	31		0.835	1.182	0.245–5.704
2-vessel disease	27		0.403	1.924	0.415–8.916
3-vessel disease	32		0.030	4.938	1.168–20.878
Left main disease [b]	8	470	<0.001	3.560	1.749–7.246

IQR=inter-quartile range; MI=myocardial infarction; ACE=angiotensin-converting enzyme; STEMI=ST-elevation myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass surgery; CAG=coronary angiography; cTnI=cardiac troponin I; ACS=acute coronary syndrome; NSTEMI=non-ST-elevation myocardial infarction; UA=unstable angina pectoris [a] Primary PCI was not used. [b] Either isolated or in association with 1-, 2- or 3-vessel disease.

investigators. Surprisingly, age and plasma creatinine level are not important. Low blood pressure at hospital admission is typical for cardiogenic shock, a state with poor short-term prognosis. This is the probable explanation for blood pressure at admission to be associated to higher mortality in multivariate analysis. Somewhat surprisingly, type 2 diabetes mellitus was not an independent predictor of prognosis. As many studies have shown Killip class to have strong predictive power, it is not surprising that previous diuretic use, a probable marker of heart failure in many patients, emerged as a strong predictor of poor prognosis.

As this was an observational study, decisions about treatment strategies concerning revascularization versus medical therapy only was left to the treating physicians. Early interventional strategy was not fully implemented at the time of the study. Revascularization was performed in 24% of the study patients during hospital stay. A benefit from an early invasive strategy in non-ST-elevation ACS has been documented in the FRISC-II and TACTICS trials (13,19). A proportionally low rate of revascularization in the acute phase of ACS may explain some of the mortality differences between randomized clinical trials and real life cohorts. Apart from noncompliance with guidelines, also the difference in age distribution between randomized studies and cohorts representing consecutive patients, may to some extent explain the difference in revascularization rates. Patients included in randomized clinical trials, like the DANAMI-2, where all patients receive reperfusion therapy, are typically younger (63 years) than those (69 years) in cohort studies like the

Table III. Variables retained in the final multivariate Cox regression model regarding mortality at follow-up (median 10 months).

Variable	Hazard ratio	95% CI	*P*-value
Age years	1.049	1.034–1.064	<0.001
Diabetes			
No diabetes	1		
Diabetes mellitus type 1	3.738	1.344–10.394	0.012
Diabetes mellitus type 2	1.180	0.904–1.540	0.225
Diuretic use on admission	1.389	1.052–1.833	<0.001
Plasma creatinine	1.003	1.002–1.005	<0.001
Systolic blood pressure	0.992	0.988–0.996	<0.001
Category of ACS			
UA	1		
STEMI	3.473	2.060–5.855	<0.001
NSTEMI	3.883	2.387–6.318	<0.001
PCI	0.595	0.355–1.000	0.050
CABG	0.562	0.304–1.041	0.067

ACS=acute coronary syndrome; UA=unstable angina pectoris; STEMI=ST-elevation myocardial infarction; NSTEMI=non-ST-elevation myocardial infarction; PCI=percutaneous coronary intervention during hospital stay; CABG=coronary artery bypass grafting during hospital stay.

present one. Clinicians may be reluctant to choose an invasive therapeutic strategy for older people, in whom data from randomized trials is scarce (20).

Primary PCI was not standard therapy in our hospital during the study. Guidelines recommending early invasive evaluation of STEMI patients have been launched only recently. There was a strong trend for PCI and CABG to have a positive prognostic impact on mortality. However, treatment allocation was not randomized and the significance of this finding needs further clarification.

In the present study 57% of STEMI patients received thrombolytic therapy at hospital admission. Studies have shown that reperfusion therapy is underutilized in acute myocardial infarction patients. In the NRMI-2 registry, only 66% of eligible patients were given fibrinolytic therapy (21). These findings are largely reproduced in Western Europe and Canada (22). The relatively low frequency of reperfusion therapy could explain some of the difference in mortality in STEMI patients in the present study compared to randomized studies.

Apart from patient selection resulting in lower-risk patients being included in randomized studies, other factors may explain differences in mortality between randomized clinical studies and real-life cohorts. Adherence of everyday clinical practice to guidelines might be unsatisfactory (22).

In conclusion, our finding that patients with STEMI or NSTEMI have higher mortality compared to what is reported in large-scale clinical trials, indicates that real world clinical scenarios might be different from what is presented in those trials. Patients enrolled in clinical trials have lower risk features and better outcomes than many patients encountered in everyday clinical practice. Hence one should be cautious when trying to extrapolate results from clinical trials to every-day practice. High-risk patients should be included in clinical trials whenever possible. All efforts should be made to optimize early risk stratification and treatment of MI patients.

Study limitations

We decided to categorize those with left bundle branch block as NSTEMI or UA patients. New (or presumably new) LBBB is considered as an indication for thrombolytic therapy. In this study it was not possible to register the proportion of new LBBB. However, only 9% of those with LBBB were treated with thrombolytic therapy supporting our decision about categorization.

Inclusion of other baseline variables, like Killip class, heart rate, pre-hospital delay from symptom onset to hospital admission and previous heart failure, could have delivered additional prognostic information.

The definition of UA varies between studies. In some studies ECG findings, like pathological Q waves, or ST-depression, or known angiographic disease, have been used as prerequisite for the diagnosis. The proportional distribution of NSTEMI versus UA in this study (57% versus 43%) was comparable to that observed in a Finnish study from nine hospitals (n=501) in 2001, where 59% of patients with non-ST-elevation ACS had elevated troponin levels (23). The UA group was proportionally smaller than the two MI patient categories because of a shorter inclusion period. Thus, its impact on the results of the multivariate analysis must be interpreted with caution. However, the authors recalculated the multivariate analysis including STEMI and NSTEMI patients, who were

included during the 'UA inclusion' period. The results were largely the same as during the whole study. As reported in the Data collection section, follow-up for the three ACS categories was different, being longest in the UA group.

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Note

Author KCN and MJE have contributed equally to the manuscript.

References

1. Salomaa V, Miettinen H, Kuulasmaa K, Niemela M, Ketonen M, Vuorenmaa T, et al. Decline of coronary heart disease mortality in Finland during 1983 to 1992: roles of incidence, recurrence, and case-fatality. The FINMONICA MI Register Study. Circulation. 1996;94:3130–7.
2. Eagle KA, Goodman SG, Avezum A, Budaj A, Sullivan CM, Lopez-Sendon J, et al. Practice variation and missed opportunities for reperfusion in ST-segment-elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet. 2002;359:373–7.
3. Hasdai D, Behar S, Wallentin L, Danchin N, Gitt AK, Boersma E, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J. 2002;23:1190–201.
4. Salomaa V, Ketonen M, Koukkunen H, Immonen-Raiha P, Jerkkola T, Karja-Koskenkari P, et al. Trends in coronary events in Finland during 1983–1997. The FINAMI study. Eur Heart J. 2003;24:311–9.
5. Andersen HR, Nielsen TT, Rasmussen K, Thuesen L, Kelbaek H, Thayssen P, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. N Engl J Med. 2003;349:733–42.
6. Topol EJ; GUSTO V Investigators. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial. Lancet. 2001;357:1905–14.
7. Barron HV, Every NR, Parsons LS, Angeja B, Goldberg RJ, Gore JM, et al. The use of intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction: data from the National Registry of Myocardial Infarction 2. Am Heart J. 2001;141:933–9.
8. Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population-based comparison. J Am Coll Cardiol. 1996;27:1335–42.
9. Armstrong PW. Coronary reperfusion: numerators searching for denominators. Lancet. 2002;359:371–2.
10. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet. 2003;361:13–20.
11. Bjorklund E, Lindahl B, Stenestrand U, Swahn E, Dellborg M, Pehrsson K, et al. Outcome of ST-elevation myocardial infarction treated with thrombolysis in the unselected population is vastly different from samples of eligible patients in a large-scale clinical trial. Am Heart J. 2004;148:566–73.
12. Terkelsen CJ, Lassen JF, Norgaard BL, Gerdes JC, Jensen T, Gotzsche LB, et al. Mortality rates in patients with ST-elevation vs. non-ST-elevation acute myocardial infarction: observations from an unselected cohort. Eur Heart J. 2005;26:18–26.
13. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. Lancet. 2000;356:9–16.
14. de Lemos JA, Blazing MA, Wiviott SD, Brady WE, White HD, Fox KA, et al. Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: results from the A phase of the A-to-Z trial. Eur Heart J. 2004;25:1688–94.
15. Goldberg RJ, Steg PG, Sadiq I, Granger CB, Jackson EA, Budaj A, et al. Extent of, and factors associated with, delay to hospital presentation in patients with acute coronary disease (the GRACE registry). Am J Cardiol. 2002;89:791–6.
16. Salomaa V, Koukkunen H, Ketonen M, Immonen-Raiha P, Karja-Koskenkari P, Mustonen J, et al. A new definition for myocardial infarction: what difference does it make? Eur Heart J. 2005;26:1719–25.
17. Roe MT, Parsons LS, Pollack CV Jr, Canto JG, Barron HV, Every NR, et al. Quality of care by classification of myocardial infarction: treatment patterns for ST-segment elevation vs non-ST-segment elevation myocardial infarction. Arch Intern Med. 2005;165:1630–6.
18. Marrugat J, Garcia M, Elosua R, Aldasoro E, Tormo MJ, Zurriaga O, et al. Short-term (28 days) prognosis between genders according to the type of coronary event (Q-wave versus non-Q-wave acute myocardial infarction versus unstable angina pectoris). Am J Cardiol. 2004;94:1161–5.
19. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med. 2001;344:1879–87.
20. Bhatt DL, Roe MT, Peterson ED, Li Y, Chen AY, Harrington RA, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. JAMA. 2004;292:2096–104.
21. Barron HV, Bowlby LJ, Breen T, Rogers WJ, Canto JG, Zhang Y, et al. Use of reperfusion therapy for acute myocardial infarction in the United States: data from the National Registry of Myocardial Infarction 2. Circulation. 1998;97:1150–6.
22. Venturini F, Romero M, Tognoni G. Patterns of practice for acute myocardial infarction in a population from ten countries. Eur J Clin Pharmacol. 1999;54:877–86.
23. Vikman S, Airaksinen KE, Tierala I, Peuhkurinen K, Majamaa-Voltti K, Niemela M, et al. Improved adherence to practice guidelines yields better outcome in high-risk patients with acute coronary syndrome without ST elevation: findings from nationwide FINACS studies. J Intern Med. 2004;256:316–23.

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ORIGINAL ARTICLE

Electrocardiographic presentation of global ischemia in acute coronary syndrome predicts poor outcome

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Abstract

Background. Global ischemia (GI) electrocardiogram (ECG), wide-spread ST depression with inverted T waves maximally in leads $V_{4–5}$, and lead aVR ST elevation (STE), is a marker of an adverse outcome in patients with non-ST elevation acute coronary syndromes (ACS), perhaps because this pattern is indicative of left main stenosis. The prognostic value of this ECG pattern has not been established.

Aims. The distribution of ECG changes and the prognostic value of the GI ECG were studied.

Methods. ECGs of consecutive patients admitted with suspected ACS (n = 1,188) were classified into seven ECG categories: STE, Q waves without STE, left bundle branch block, left ventricular hypertrophy, GI ECG, other ST depression and/or T wave inversion, and other findings.

Results. The GI ECG pattern predicted a high rate (48%) of composite end-points (mortality, re-infarction, unstable angina, resuscitation, or stroke) at 10-month follow-up compared to the other ECG categories (36%) (HR 1.78; CI 95% 1.31–2.41; $P < 0.001$). In multivariate analysis, the GI ECG pattern was associated with a higher rate of composite end-points (HR 1.40; CI 95% 1.02–1.91; $P = 0.035$). The multivariate analysis furthermore identified age, creatinine level, and diabetes as independent predictors of prognosis.

Conclusions. The GI ECG pattern predicted an unfavorable outcome, when compared to other ECG patterns in patients with ACS.

Key words: *Acute coronary syndrome, electrocardiogram, left main disease*

Introduction

The electrocardiogram (ECG) is the most accessible and widely used diagnostic tool for patients with symptoms suggestive of acute myocardial ischemia. Although the presence of acute ischemic changes on the admission ECG has been associated with a higher risk of cardiac events, the prognostic value of the various ECG presentations of acute myocardial ischemia remains elusive (1–5).

As left main (LM) coronary artery disease is associated with high mortality, early diagnosis is important (6). Accordingly, ST depression and lead aVR ST elevation have been established as ECG markers of an adverse outcome in non-ST elevation acute coronary syndrome (ACS) (7–10). ST depression with inverted T waves in the precordial leads in patients without tachycardia was associated with LM disease in rather small studies (11–13). In one of these studies, one-quarter of the patients showing this ECG pattern proved to have severe three-vessel disease, while three-quarters had LM or LM-equivalent disease on coronary angiography (13). The ECG pattern with wide-spread ST depression and inverted T waves maximally in leads $V_{4–5}$ has been ascribed to circumferential subendocardial ischemia (14). Lead aVR ST elevation is a typical finding in

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Key messages

- The global ischemia ECG pattern with wide-spread ST depression, maximally in leads $V_{4–5}$ with inverted T waves and ST elevation in lead aVR, predicts poor prognosis compared to other ECG patterns in patients with acute coronary syndrome.
- Further studies are needed to confirm whether coronary angiography should be considered in urgent cases with ECG signs of global ischemia.

Abbreviations

ACS	acute coronary syndrome
CI	confidence interval
ECG	electrocardiogram
HR	hazard ratio
LBBB	left bundle branch block
LM	left main
LVH	left ventricular hypertrophy
RBBB	right bundle branch block
TACOS	Tampere Acute COronary Syndrome

these patients (Figure 1). The prognostic value of this ECG pattern, the 'global ischemia ECG' pattern, consisting of wide-spread ST depression and inverted T waves maximally in leads $V_{4–5}$ and lead aVR ST elevation, in comparison to other ECG manifestations of ACS, has not been studied.

In the present study we investigated the distribution and prognostic impact of seven predefined ECG patterns in ECGs from patients admitted with ACS. The ECG patterns were: ST elevation, pathological Q waves, left bundle branch block (LBBB), left ventricular hypertrophy (LVH), global ischemia ECG, other ST depression and/or T wave inversion, and other findings, including normal ECG.

Material and methods

Patients

Patients presenting with presumptive diagnosis of ACS at admission to the emergency department were consecutively included in the study. The study was performed at Tampere University Hospital, and 1,188 patients were included between 1 January 2002 and 31 March 2003. A total of 343 presented with ST elevation myocardial infarction, 655 with non-ST elevation myocardial infarction, and 190 with unstable angina. The study end-point was a composite of mortality, re-infarction, unstable angina, resuscitation, or stroke in hospital and during 10-month follow-up. The detailed description of the protocol of the TACOS (Tampere Acute COronary Syndrome) study has been reported previously (15).

The Ethics Committee at Tampere University Hospital approved the study protocol. The patients gave their written informed consent for participation.

ECG analysis

The incidence at hospital admission and the patient prognosis based on the ECG patterns were studied. The investigators analyzed the patient ECG recorded

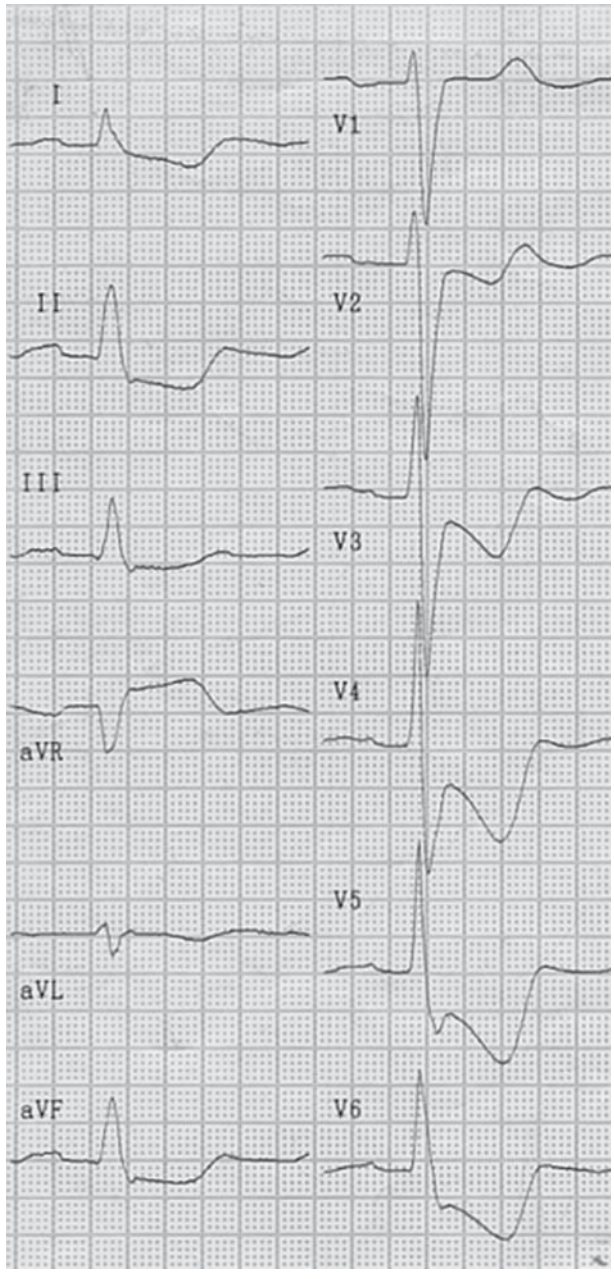

Figure 1. ECG (50 mm/s) shows the global ischemia ECG pattern: ST depression and inverted T waves maximally in leads $V_{4–5}$ and ST elevation in lead aVR.

either pre-hospitally or in the emergency department showing maximal ischemic changes. If the ECG in the referral unit was normal, but a follow-up ECG in the emergency department showed ST deviation, the second one was used for analysis. No ECGs recorded during hospital stay—for example, in the coronary care unit or in the catheterization laboratory—were used. All the ECGs were analyzed by two investigators (KCN and MJE) blinded to the clinical data. The patients were classified into seven predefined ECG categories: 1) ST elevation (elevation of the ST segment ≥2 mm in two contiguous precordial leads or ≥1 mm in two contiguous limb leads); 2) pathological Q waves without ST elevation (defined as A: in leads $V_{1–3}$ any Q wave ≥30 ms in duration; B: in leads I, II, aVL, aVF, $V_{4–6}$ a Q wave ≥1 mm and ≥30 ms in duration in ≥2 adjacent leads; and C: 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 (RBBB)); 3) typical LBBB; 4) LVH without ST elevation except in leads aVR and/or V_1 (LVH was defined according to the Sokolow–Lyon criteria (16) and/or the Cornell voltage-duration product (17); 5) global ischemia ECG (ST depression ≥0.5 mm in ≥6 leads, maximally in leads $V_{4–5}$ with inverted T waves and ST elevation ≥0.5 mm in lead aVR) (Figure 1); 6) other ST depression and/or T wave inversion; and 7) other findings, including normal ECG.

The classification into the ECG categories was based solely on the actual ECG. No comparison to previous ECGs was done.

The ST segment, determined by drawing a line between subsequent PR segments, and measured 0.06 s after the J point, was considered elevated or depressed if it was 0.5 mm or more above or below the isoelectric line, respectively. The T wave was considered positive or negative if it was 1 mm or more above or below the isoelectric line, measured more than 120 ms after the J point with the aid of a hand-held magnifying lens.

Statistical analysis

Categorical variables were expressed as numbers of patients or percentages and continuous variables as medians followed by interquartile range. We used the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney test for numerical variables. A two-tailed *P* value of <0.05 was considered statistically significant. Confidence intervals (CI) were calculated at the 95% significance level. Composite end-point data between ECG categories were plotted as Kaplan–Meier curves. Comparison between the ECG groups was made using the log rank statistic. Hazard ratios (HR) were calculated by Cox regression analysis. Variables with $P < 0.20$ in the Cox univariate analysis were included in the multivariate Cox regression model. Age and gender adjustment was included. All calculations were performed with the SPSS 16.0 statistical package.

Results

Our study showed differences between groups of patients stratified according to ECG categories both in base-line characteristics and in-hospital findings (Tables I and II). Among the seven categories, ST elevation proved to be the most frequent, followed by old Q waves without ST elevation (Figure 2). Patients with global ischemia ECG, LBBB, and LVH were older than those from the four other categories, while patients with global ischemia ECG more often had hypertension, diabetes, prior angina, and severe anginal symptoms. They were also more often on aspirin, beta-blocker, nitrate, and diuretic medication. Systolic dysfunction based on echocardiographic ejection fraction measurement was more often seen in patients with LBBB and old Q waves. Patients with other ST depression and/or T wave inversion had the lowest troponin levels.

Coronary angiography during the hospital stay was performed in 560 patients (47%). The patients with global ischemia ECG had more severe disease on coronary angiography compared to the other ECG categories (Table II). All the patients with global ischemia ECG, in whom angiography was performed, showed significant coronary artery disease, and this ECG pattern was associated with angiographic three-vessel disease in 71%. LM disease either isolated or in association with one-, two-, or three-vessel disease was present in 25% of the patients. The corresponding numbers for other ST depression and/or T wave inversion was only 22% for three-vessel disease and 3% for LM disease. Revascularization during hospital stay was more frequent in patients with global ischemia ECG than in patients from the other ECG categories.

In univariate analysis, in-hospital mortality rate was highest among patients with LBBB and global ischemia ECG (18% and 14%, respectively; $P = 0.004$). The incidence of in-hospital composite end-points was lowest in patients with LVH, ST elevation, and ST depression and/or T wave inversion (12%, 16%, and 14%, respectively; $P = 0.009$).

The global ischemia ECG pattern predicted a high rate of composite end-points (48%) at 10-month follow-up compared to all the other ECG categories (36%) (HR 1.78; CI 1.31–2.41; $P < 0.001$) (Figure 3). In multivariate analysis, global ischemia ECG pattern, age, creatinine level at presentation, and diabetes

Table I. Base-line characteristics according to electrocardiographic classification.

Base-line characteristics	STE $n = 349$ n (%)	STD and/or T-inv $n = 160$ n (%)	GI-ECG $n = 97$ n (%)	LBBB $n = 71$ n (%)	LVH $n = 82$ n (%)	Q wave $n = 272$ n (%)	Other ECG changes $n = 157$ n (%)	P value
Age (y)[a]	68 (56–77)	72 (59–79)	77 (71–84)	77 (71–84)	77 (71–84)	73 (64–80)	72 (64–79)	<0.001
Gender (males)	225 (65)	77 (48)	42 (43)	34 (48)	39 (48)	181 (67)	96 (61)	<0.001
Hypertension	175 (50)	88 (56)	60 (63)	42 (59)	51 (62)	136 (51)	81 (52)	0.16
Diabetes	79 (23)	36 (23)	32 (33)	22 (31)	15 (18)	70 (26)	49 (31)	0.13
Current smoker	83 (25)	30 (20)	10 (12)	3 (5)	9 (13)	55 (22)	14 (10)	<0.001
Previous MI	53 (15)	28 (18)	30 (31)	19 (27)	21 (26)	93 (35)	44 (28)	<0.001
Previous PCI or CABG	34 (10)	19 (12)	12 (12)	13 (19)	10 (12)	33 (12)	33 (21)	0.02
Prior angina (>3 months)	116 (36)	69 (48)	50 (60)	25 (46)	44 (60)	108 (46)	72 (55)	<0.001
CCS class								<0.001
1–2	91 (28)	54 (37)	31 (37)	19 (35)	33 (45)	82 (35)	53 (41)	
3–4	25 (8)	15 (11)	19 (23)	6 (11)	11 (15)	26 (11)	19 (14)	
Systolic blood pressure (mmHg) [a]	144 (126–166)	150 (132–172)	144 (122–170)	146 (124–160)	160 (143–189)	141 (121–161)	145 (122–168)	<0.001
Medical treatment								
Aspirin	124 (36)	72 (45)	54 (56)	32 (46)	41 (40)	124 (46)	83 (53)	0.001
Clopidogrel	4 (1)	2 (1)	1 (1)	1 (1)	0	2 (1)	2 (1)	0.96
Beta-blockers	142 (41)	87 (54)	65 (67)	35 (49)	45 (55)	135 (50)	78 (50)	<0.001
ACE inhibitors	53 (15)	26 (16)	27 (28)	23 (33)	19 (23)	69 (25)	40 (26)	0.001
ARB	18 (5)	13 (8)	5 (5)	6 (9)	11 (13)	21 (8)	9 (6)	0.20
Calcium antagonists	70 (20)	35 (22)	27 (28)	16 (23)	16 (20)	45 (17)	39 (25)	0.24
Digitalis	18 (5)	15 (9)	18 (19)	19 (27)	25 (31)	29 (11)	20 (13)	<0.001
Nitrates	117 (34)	75 (47)	69 (71)	48 (66)	44 (54)	128 (47)	84 (54)	<0.001
Diuretics	68 (20)	49 (31)	49 (51)	42 (59)	37 (45)	94 (35)	62 (40)	<0.001
Statin	65 (19)	47 (29)	26 (27)	14 (20)	17 (21)	55 (20)	38 (24)	0.13
Warfarin	21 (6)	17 (11)	15 (16)	17 (24)	12 (15)	38 (14)	23 (15)	<0.001

[a]Variables are given as median values followed by interquartile ranges.

STE = ST elevation; STD = ST depression; T-inv = T wave inversion; GI = global ischemia; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; ECG = electrocardiogram; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass surgery; CCS = Canadian Cardiovascular Society; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.

Table II. In-hospital findings, treatment, and outcome by electrocardiographic categories. Medication at discharge.

Base-line characteristics	STE $n = 349$ n (%)	STD and/or T-inv $n = 160$ n (%)	GI-ECG $n = 97$ n (%)	LBBB $n = 71$ n (%)	LVH $n = 82$ n (%)	Q wave $n = 272$ n (%)	Other ECG changes $n = 157$ n (%)	P value
Plasma creatinine (μmol/L)[a]	84 (72–99)	81 (67–99)	92 (75–115)	100 (81–127)	90 (71–120)	90 (75–112)	93 (73–114)	<0.001
C-reactive protein (mg/L)[a]	1 (3–37)	9 (2–50)	19 (4–67)	14 (5–67)	16 (4–68)	22 (5–69)	8 (3–31)	<0.001
cTnI (μg/L)[a]	15 (2–61)	1 (0–5)	7 (1–20)	2 (0.7–13)	2 (0.5–7)	7 (1–39)	1 (0–10)	<0.001
Ejection fraction[a]	60 (48–70)	60 (48–70)	60 (45–70)	40 (32–60)	51 (41–63)	45 (36–60)	55 (45–70)	<0.001
CAG data available	207 (59)	70 (44)	48 (49)	24 (34)	27 (33)	122 (45)	62 (39)	
Number of diseased vessels[b]								<0.001
<50% stenosis	17 (8)	20 (29)	0	7 (29)	4 (15)	8 (7)	13 (21)	
One-vessel disease	82 (40)	20 (29)	4 (8)	6 (25)	2 (7)	31 (25)	22 (36)	
Two-vessel disease	64 (31)	14 (20)	10 (21)	2 (8)	6 (22)	36 (30)	13 (21)	
Three-vessel disease	44 (21)	16 (22)	34 (71)	9 (38)	15 (56)	47 (38)	14 (22)	
Left main disease[c]	6 (3)	2 (3)	12 (25)	5 (21)	4 (15)	12 (10)	3 (5)	<0.001
PCI or CABG	112 (32)	27 (17)	60 (62)	8 (11)	10 (12)	58 (21)	28 (18)	<0.001
In-hospital event								
Composite end-points[d]	54 (16)	22 (14)	28 (30)	15 (21)	10 (12)	58 (21)	36 (23)	0.009
Death	23 (7)	13 (8)	14 (14)	13 (18)	4 (5)	34 (13)	22 (14)	0.004
Medication at discharge								
Aspirin	328 (94)	141 (88)	80 (83)	55 (78)	71 (87)	241 (89)	128 (82)	<0.001
Clopidogrel	114 (33)	29 (18)	16 (17)	6 (9)	9 (11)	43 (16)	22 (14)	<0.001
Beta-blockers	329 (94)	148 (93)	93 (96)	64 (90)	77 (94)	256 (94)	137 (87)	0.07
ACE inhibitors	163 (47)	56 (35)	38 (39)	43 (61)	37 (45)	159 (59)	54 (34)	<0.001
ARB	20 (6)	16 (10)	6 (6)	5 (7)	10 (12)	21 (8)	10 (6)	0.16
Calcium antagonists	54 (16)	32 (20)	25 (26)	14 (20)	22 (27)	35 (13)	36 (23)	0.008
Digitalis	27 (8)	17 (11)	30 (31)	19 (27)	26 (32)	49 (18)	25 (16)	<0.001
Nitrates	251 (72)	103 (64)	81 (84)	52 (73)	65 (79)	204 (75)	104 (66)	0.009
Diuretics	153 (44)	80 (50)	87 (90)	59 (83)	63 (77)	187 (69)	92 (59)	<0.001
Statin	253 (73)	86 (54)	58 (60)	25 (35)	36 (44)	146 (54)	73 (47)	<0.001
Warfarin	58 (17)	33 (21)	22 (23)	28 (39	25 (31)	90 (33)	32 (20)	<0.001

[a]Variables are given as median values followed by interquartile ranges.
[b]Stenosis diameter 50% or more considered as significant.
[c]Either isolated or in association with one-, two-, or three-vessel disease.
[d]Death, resuscitation, re-infarction, unstable angina, or stroke.
STE = ST elevation; STD = ST depression; T-inv = T wave inversion; GI = global ischemia; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; ECG = electrocardiogram; cTnI = cardiac troponin I; CAG = coronary angiography; PCI = percutaneous coronary intervention; CABG = coronary artery bypass surgery; ARB = angiotensin receptor blockers.

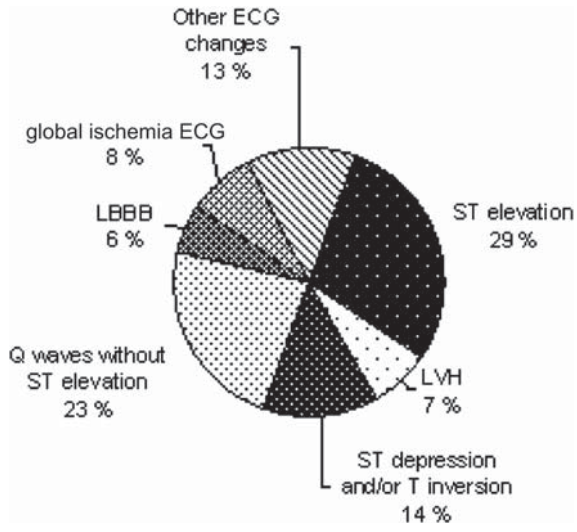

Figure 2. Distribution of ECG changes of all consecutive patients admitted with acute coronary syndrome. Rates are based on the TACOS study, $n = 1{,}188$.

were identified as independent predictors for poor prognosis at 10-month follow-up (Table III).

Discussion

This study adds new interesting data about prognostic and therapeutic differences between distinct ECG findings on hospital admission in patients with ACS. Our study shows that the global ischemia ECG pattern, consisting of concomitant ST depression with inverted T waves maximally in leads $V_{4–5}$ and ST elevation in lead aVR (Figure 1), is associated with worse prognosis than other ECG patterns.

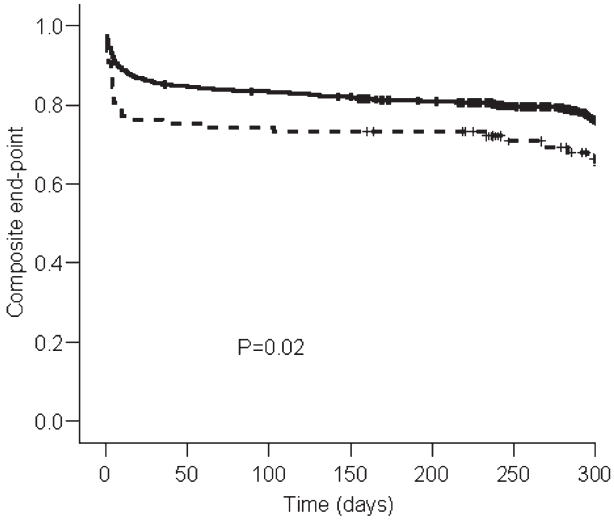

Figure 3. The rate of composite end-points at 10-month follow-up according to the ECG at admission presented by the Kaplan–Meier curve (dashed line: global ischemia ECG, solid line: all other ECG categories).

Our study population represents consecutive patients of all the three categories of ACS, ST elevation and non-ST elevation acute myocardial infarction, and unstable angina. Patients in randomized clinical trials tend to be younger than those in unselected patient cohorts. In a pooled analysis of large randomized trials of ACS therapies, only 18% of the 34,266 patients enrolled were ≥75 years old (18). Of the more than 11,000 patients included in the multinational prospective Global Registry of Acute Coronary Events (GRACE) study, more than 30% of the patients were ≥75 years old (19). In the present study the median age for the patients in the seven ECG categories varied between 68 and 77 years. Hence, this represents a study population typically encountered in everyday clinical work. The GRACE registry study and our study showed similar proportions of patients with ST elevation in the ECG at presentation. Interestingly, we found that more than one-third of the patients with ST depression presented with the global ischemia ECG pattern. Normal ECG was found in 13% of the patients included in this study. This probably reflects that patients with unstable angina without elevated biomarkers of myocardial injury ($n = 190$) were included. Previous studies have reported incidences of up to 18.5% with normal ECG in patients with acute myocardial infarction (3).

According to previous studies in non-ST elevation ACS, all the three global ischemia ECG components, ST depression, T wave inversion, and lead aVR ST elevation, were associated with higher mortality. Despite that the global ECG pattern has not previously been investigated, the different components of the pattern have all been studied separately and support our findings. ST depression and T wave inversion in leads $V_{4–6}$ have been found to predict

Table III. Variables retained in the final multivariate Cox proportional hazards model examining the rate of composite end-points at 10-month follow-up.

	Hazard ratio	95% CI	*P* value
Age	1.04	1.03–1.05	<0.001
Global ischemia ECG pattern	1.40	1.02–1.91	0.035
Gender	1.10	0.90–1.36	0.363
Systolic blood pressure	0.97	0.94–1.00	0.053
Plasma creatinine	1.003	1.002–1.004	<0.001
Diabetes	1.48	1.07–2.05	0.017
No diabetes	1		
Diabetes mellitus type I	2.65	1.16–6.07	0.021
Diabetes mellitus type II	1.12	0.91–1.39	0.227
Diuretic use on admission	1.24	0.998–1.54	0.052

CI = confidence interval; ECG = electrocardiogram.

1-year mortality independently (1). Another study found that the presence, magnitude, and extent of ST depression were associated with increased mortality in patients with non-ST elevation myocardial infarction (5). Interestingly, ST depression in two or more lateral (I, aVL, V_5, or V_6) leads proved to be the only ECG variable that predicted death after adjusting for base-line predictors. Patients with lateral ST depression had higher rates of death and severe heart failure than did the remaining patients, even though they had similar enzyme levels. In contrast, ST depression not involving the lateral leads did not predict poor outcome. The authors did not include T waves in their analyses. One could speculate that the poor outcome in patients with lateral ST depression was associated with the global ischemia ECG pattern described in our study.

ST elevation in lead aVR in the setting of ACS has been established as a marker of severe coronary artery disease and worse outcome. In a small study, Yamaji et al. compared the ECG findings of patients with acute LM obstruction with the findings of patients with acute left anterior descending or right coronary artery obstruction (20). Lead aVR ST elevation >0.5 mm was markedly more frequent in the patients with LM obstruction than in the two other groups, and the patients who died during follow-up had higher levels of ST elevation in lead aVR than the survivors. The authors did not focus on possible ST depression. The HERO-2 investigators recently reported aVR ST elevation ≥1 mm to be associated with higher 30-day mortality in both anterior and inferior acute ST elevation myocardial infarction (21). After adjusting for summed ST elevation and ST depression in other leads, associations with higher mortality were found with aVR ST elevation of ≥1.5 mm for anterior and of ≥1 mm for inferior ST elevation myocardial infarction. Notably, when adjustment was made for clinical factors, the association between aVR ST elevation and 30-day mortality lost its significance. This underlines the importance of recognizing the complete ECG pattern in myocardial ischemia and not only changes in one lead when assessing patient risk. In a recent systematic review article, the absence of aVR ST elevation appeared to exclude LM stenosis as the underlying cause in non-ST elevation myocardial infarction (22).

Sclarovsky and associates introduced the concept of T wave inversion in combination with lateral ST depression as a risk marker in ACS without ST elevation (11). They studied 32 consecutive patients who had horizontal or downward-sloping ST depression with peaked (n = 21) or inverted (n = 11) T waves. In the group with inverted T waves, the in-hospital mortality was 27%, whereas none of the patients with positive T waves died in the hospital. In addition, seven out of ten patients with inverted T waves had significant LM disease on angiography, while two out of ten patients had three-vessel disease.

We have earlier reported that patients (n = 25) with transient ST depression and an inverted T wave maximally in leads $V_{4–5}$ during anginal pain had higher in-hospital mortality (24%) than patients (n = 25) with ST depression and a positive T wave (0%) (13). In that study, all the patients with ST depression and inverted T waves also had ST elevation of at least 0.5 mm in lead aVR.

The exact electro/pathophysiologic mechanisms of the global ischemia ECG are not known. When myocardial ischemia is confined primarily to the subendocardium, the overall ST vector typically faces the inner ventricular layer and the ventricular cavity, such that the surface ECG leads show ST depression (23). This subendocardial ischemic pattern represents the typical ECG finding during exercise tests, as energy demands are highest and blood supply most precarious in the inner layers of the myocardium (24). In these cases, extensive ischemia impairs relaxation of the left ventricle, resulting in increase of the left ventricular end-diastolic pressure (25). Inducing global left ventricular ischemia in dogs by hydraulic constriction of the LM resulted in a significant decrease in the endocardial-to-epicardial flow ratio and a significant increase of left ventricular end-diastolic pressure (26). Also, inducing elevation of the left ventricular pressure by pacing in patients with significant coronary artery disease was associated with ST depression in the ECG (27). Hence, we speculate that the global ischemia ECG represents the electrical effects of severe subendocardial ischemia, which generates an ST vector that points away from the apical/lateral leads $V_{4–5}$ and towards lead aVR. In the present study, of the patients with global ischemia ECG, in which angiography was performed, almost three-quarters had angiographic three-vessel disease, while one-quarter had LM disease either isolated or in association with one-, two-, or three-vessel disease.

The present and above-mentioned studies reveal that different manifestations of ST/T changes have significantly different prognostic implications. Still, in the modern era of high technology, the ECG has a central role in clinical decision-making in ACS. We think that much is to be gained by extending the ECG analysis beyond ST elevation and non-ST elevation categories.

Limitations

There are quite a few study limitations to be reported in this study. The proportion of patients

having coronary angiography was less than 50%. Accordingly, correlation between ECG and angiographic data cannot be reliably calculated. However, our primary aim was to study differences in outcome between the ECG categories, not to correlate with angiographic findings. Another possible limitation is the fact that the magnitude of ST elevation in lead aVR was not used in our statistical analyses. This could be included in future prospective trials.

Base-line data regarding Killip class and heart rate were not included in the statistical analyses. Neither were data on delay from symptom onset to ECG recording. Echocardiographic findings were not available for all patients.

Conclusion

We have identified a high-risk ECG pattern in patients categorized as non-ST elevation ACS. The ECG pattern with wide-spread ST depression, maximally in leads $V_{4–5}$, with inverted T waves and ST elevation in lead aVR was present in 8% of 'all-comers' with ACS. This global ischemia ECG pattern predicted poor prognosis compared to other ECG patterns and was independently associated with an adverse outcome in multivariate analysis. From the therapeutic point of view, it is justified to conclude that future studies are needed to test whether urgent cases with ECG signs of severe coronary artery disease should have coronary angiography on an emergency basis. Besides the high rate of need for urgent revascularization there is a high probability for a composite of mortality, re-infarction, unstable angina, resuscitation, or stroke in hospital or at follow-up compared to other ECG patterns.

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References

1. Atar S, Fu Y, Wagner GS, Rosanio S, Barbagelata A, Birnbaum Y. Usefulness of ST depression with T-wave inversion in leads V(4) to V(6) for predicting one-year mortality in non-ST-elevation acute coronary syndrome (from the electrocardiographic analysis of the global use of strategies to open occluded coronary arteries IIB trial). Am J Cardiol. 2007;99:934–8.
2. Cannon CP, McCabe CH, Stone PH, Rogers WJ, Schactman M, Thompson BW, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: Results of the TIMI III registry ECG ancillary study. Thrombolysis in myocardial ischemia. J Am Coll Cardiol. 1997;30:133–40.
3. Miller WL, Sgura FA, Kopecky SL, Asirvathan SJ, Williams BA, Wright RS, et al. Characteristics of presenting electrocardiograms of acute myocardial infarction from a community-based population predict short- and long-term mortality. Am J Cardiol. 2001;87:1045–50.
4. Savonitto S, Ardissino D, Granger CB, Morando G, Prando MD, Mafrici A, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA. 1999;281:707–13.
5. Barrabes JA, Figueras J, Moure C, Cortadellas J, Soler-Soler J. Prognostic significance of ST segment depression in lateral leads I, aVL, V5 and V6 on the admission electrocardiogram in patients with a first acute myocardial infarction without ST segment elevation. J Am Coll Cardiol. 2000;35:1813–9.
6. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, et al. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. Circulation. 1995;91:2335–44.
7. Kaul P, Fu Y, Chang WC, Harrington RA, Wagner GS, Goodman SG, et al. Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. PARAGON-A and GUSTO IIb Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network. J Am Coll Cardiol. 2001;38:64–71.
8. Holmvang L, Clemmensen P, Lindahl B, Lagerqvist B, Venge P, Wagner G, et al. Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. J Am Coll Cardiol. 2003;41:905–15.
9. Savonitto S, Cohen MG, Politi A, Hudson MP, Kong DF, Huang Y, et al. Extent of ST-segment depression and cardiac events in non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2005;26:2106–13.
10. Barrabés JA, Figueras J, Moure C, Cortadellas J, Soler-Soler J. Prognostic value of lead aVR in patients with a first non-ST-segment elevation acute myocardial infarction. Circulation. 2003;108:814–9.
11. Sclarovsky S, Rechavia E, Strasberg B, Sagie A, Bassevich R, Kusniec J, et al. Unstable angina: ST segment depression with positive versus negative T wave deflections—clinical course, ECG evolution, and angiographic correlation. Am Heart J. 1988;116:933–41.
12. Nikus KC, Eskola MJ. The ECG in a mechanical obstruction of the ostium of the left main coronary artery. Int J Cardiol. 2002;86:327–9.
13. Nikus KC, Eskola MJ, Virtanen VK, Vikman S, Niemelä KO, Huhtala H, et al. ST-depression with negative T waves in leads V4-V5—a marker of severe coronary artery disease in non-ST elevation acute coronary syndrome: A prospective study of angina at rest, with troponin, clinical, electrocardiographic, and angiographic correlation. Ann Noninvasive Electrocardiol. 2004;9:207–14.
14. Sclarovsky S. Angina at rest and acute myocardial ischaemia. In: Sclarovsky S, editor. Electrocardiography of acute myocardial ischaemic syndromes. 1st ed. London, UK: Martin Dunitz Ltd; 1999. p. 1–29.
15. Nikus KC, Eskola MJ, Virtanen VK, Harju J, Huhtala H, Mikkelsson J, et al. Mortality of patients with acute coronary syndromes still remains high: A follow-up study of 1188 consecutive patients admitted to a university hospital. Ann Med. 2007;39:63–71.

16. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J. 1949;37:161–86.
17. Norman JE Jr, Levy D. Improved electrocardiographic detection of echocardiographic left ventricular hypertrophy: results of a correlated data base approach. J Am Coll Cardiol. 1995;26: 1022–9. Erratum in: J Am Coll Cardiol. 1996;27:516.
18. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007;115:2549–69.
19. Steg PG, Goldberg RJ, Gore JM, Fox KA, Eagle KA, Flather MD, et al. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). Am J Cardiol. 2002; 90:358–63.
20. Yamaji H, Iwasaki K, Kusachi S, Murakami T, Hirami R, Hamamoto H, et al. Prediction of acute left main coronary artery obstruction by 12-lead electrocardiography. ST segment elevation in lead aVR with less ST segment elevation in lead V(1). J Am Coll Cardiol. 2001;38:1348–54.
21. Wong CK, Gao W, Stewart RA, Benatar J, French JK, Aylward PE, et al. aVR ST elevation: an important but neglected sign in ST elevation acute myocardial infarction. Eur Heart J. 2010;15:1845–53.
22. Kühl JT, Berg RM. Utility of lead aVR for identifying the culprit lesion in acute myocardial infarction. Ann Noninvasive Electrocardiol. 2009;14:219–25.
23. Cook RW, Edwards JE, Pruitt RD. Electrocardiographic changes in acute subendocardial infarction. I. Large subendocardial and large nontransmural infarcts. Circulation. 1958;18:603–12.
24. Nikus K, Pahlm O, Wagner G, Birnbaum Y, Cinca J, Clemmensen P, et al. Electrocardiographic classification of acute coronary syndromes: A review by a committee of the international society for holter and non-invasive electrocardiology. J Electrocardiol. 2010;43:91–103.
25. Grossman W. Evaluation of systolic and diastolic function of the ventricles and myocardium. In: Baim DS, Grossman W, editors. Grossman's cardiac catheterization, angiography and intervention. 6th ed. Philadelphia, Pa: Lippincott Williams and Wilkins; 2001. p. 367–90.
26. Visner MS, Arentzen CE, Parrish DG, Larson EV, O'Connor MJ, Crumbley AJ 3rd, et al. Effects of global ischemia on the diastolic properties of the left ventricle in the conscious dog. Circulation. 1985;71:610–9.
27. Aroesty JM, McKay RG, Heller GV, Royal HD, Als AV, Grossman W. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. Circulation. 1985;71:889–900.

Electrocardiographic Presentation of Left Main Disease in Patients Undergoing Urgent or Emergent Coronary Artery Bypass Grafting

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Abstract

Background: Widespread ST-segment depression with inverted T waves maximally in leads V_4–V_5 (ie, the global ischemia electrocardiogram [ECG] pattern) is a marker of adverse outcome in patients with non–ST-segment elevation acute coronary syndrome (ACS), perhaps because this pattern is indicative of left main stem stenosis. However, the prognostic value of this ECG pattern has not yet been established. **Objective:** We studied the predictive value of a prespecified ECG pattern in patients who underwent urgent or emergent coronary artery bypass grafting (CABG). **Methods:** We studied the sensitivity, specificity, and predictive values for the global ischemia ECG to predict angiographic left main coronary artery disease. Patients with a 12-lead ECG recorded during anginal symptoms before CABG were included. **Results:** The global ischemia ECG pattern was found in 61 (76%) of 80 patients with and 12 (19%) of 65 patients without left main disease. The sensitivity, specificity, and positive and negative predictive values for left main coronary artery disease in patients with the global ischemia ECG pattern were 76%, 81%, 84%, and 74%, respectively. In multivariate analysis, the global ischemia ECG pattern was strongly associated with angiographic left main coronary artery disease after adjusting for age, gender, diabetes, hypertension, and smoking (hazard ratio, 16.0; 95% confidence interval, 6.5–39.5; $P < 0.001$). **Conclusion:** The global ischemia ECG pattern was strongly associated with angiographic left main coronary artery disease in patients who underwent urgent or emergent CABG.

Keywords: acute coronary syndrome; electrocardiogram; left main coronary artery disease; bypass grafting

Introduction

The electrocardiogram (ECG) is the most accessible and widely used diagnostic tool for patients with symptoms suggestive of acute myocardial ischemia. Although the presence of acute ischemic changes on admission ECG has been associated with a higher risk of cardiac events, the prognostic implications of the different ECG presentations of acute myocardial ischemia are not well defined.[1–5] The ECG is a promising tool to identify high-risk patients, but larger studies are needed to evaluate the diagnostic and prognostic impact of the different ischemia ECG patterns in patients with acute coronary syndrome (ACS).[6]

It is important to identify patients with left main (LM) coronary artery disease using noninvasive methods[7] because these are associated with high mortality. Patients who have isolated coronary artery bypass grafting (CABG) on an urgent or emergent basis have severe coronary artery disease. The ECG manifestations of this patient group have not been well established.

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ST-segment depression and lead aVR ST-segment elevation have been established as ECG markers of worse outcome in non–ST-segment elevation ACS.[8–11] ST-segment depression with inverted T waves in the precordial leads in patients without tachycardia was associated with LM coronary artery disease in small studies.[12–14] The ECG pattern with widespread ST-segment depression and inverted T waves maximally in leads V_4–V_5 has been described by Sclarovsky[15] as circumferential subendocardial ischemia. Lead aVR ST-segment elevation is a typical finding in these patients (Figure 1A, B). The prognostic value of this ECG pattern, the "global ischemia ECG" pattern, in comparison with other ECG manifestations of ACS, has not been studied.

The aim of our study was to compare preoperative 12-lead ECG findings during anginal pain in patients with and without LM coronary artery disease who underwent isolated urgent or emergent CABG. Specifically, we studied the sensitivity, specificity, and predictive values for the global ischemia ECG pattern recorded during anginal symptoms before CABG to predict angiographic LM coronary artery disease.

Materials and Methods

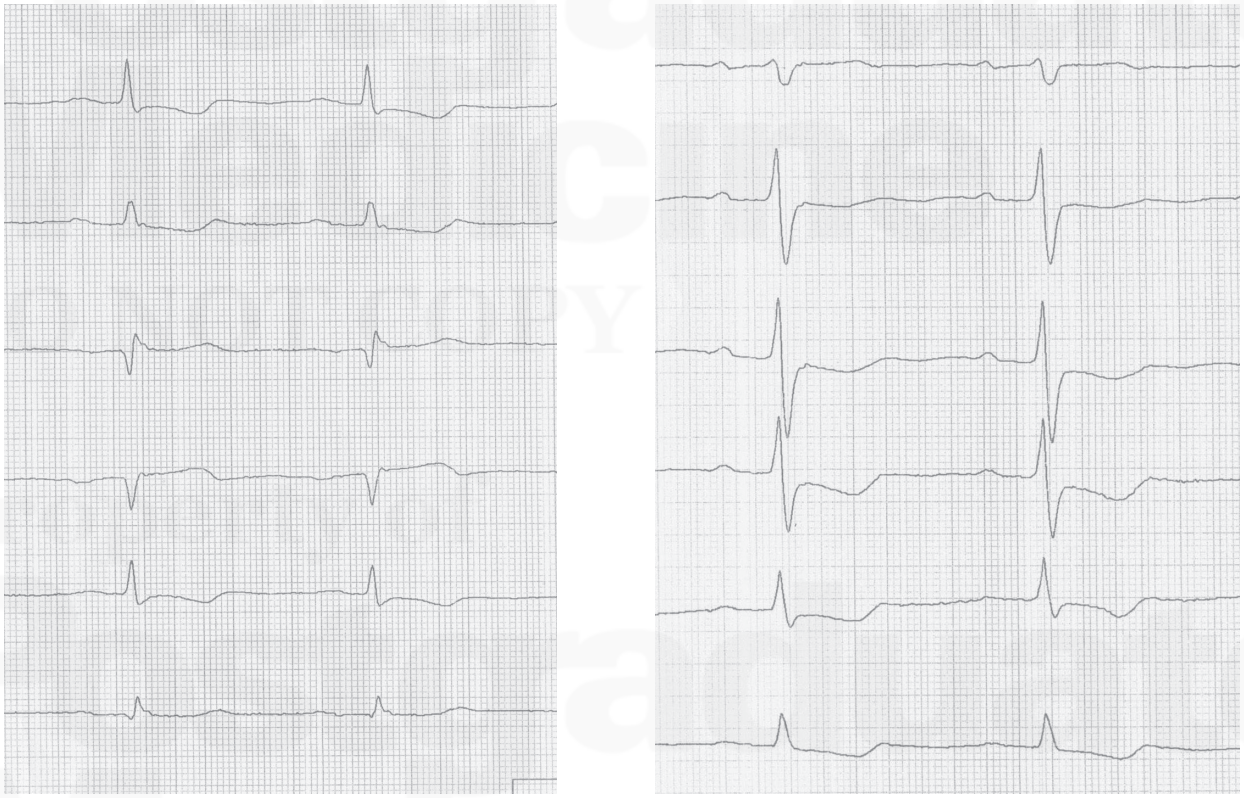
Patients

The detailed description of the protocol of the original study has been reported previously.[16] Isolated CABG was performed in 1131 patients in Tampere University Hospital (Tampere, Finland) between May 2, 1999 and November 30, 2000.

For the present study, the inclusion criteria were the existence of a preoperative 12-lead ECG recorded during anginal symptoms, significant LM stem stenosis on angiogram, and urgent or emergent CABG performed during the hospital stay. Of the 1131 patients who had isolated CABG, 442 patients had an urgent (n = 400) or emergent (n = 42) procedure. Of these patients, 132 had significant LM stem stenosis (LM+ group). For the control group, we randomly chose 132 patients who also underwent urgent or emergent CABG but who had no significant LM stem stenosis on angiography (LM– group). Patient files and ECGs from the LM+ and the LM– groups were analyzed. A total of 80 (61%) of 132 patients from the LM+ group and 65 (49%) of 132 patients

Figure 1A. Extremity leads I, II, III, aVR, aVL, and aVF.

Figure 1B. Precordial leads V_1–V_6.



Electrocardiogram (50 mm/sec) recorded during anginal pain in a patient with left main coronary artery disease, showing circumferential subendocardial ischemia ("global ischemia"). ST-segment depression is seen in leads I, II, aVL, and V_2–V_6. The maximal ST-segment depression is in lead V_4, and the T waves are inverted in leads V_4–V_5. The ST segment is elevated in lead aVR.

from the LM– group were included in the final study group. Table 1 shows the reasons for patient exclusion.

Level of significance of LM stem stenosis was defined as ≥ 50% diameter stenosis. The study was approved by the institutional review board of Tampere University Hospital, and all patients gave their written informed consent for participation.

ECG Analysis

All in-hospital and, if applicable, pre-hospital admission ECGs recorded within 6 months before CABG of both patient groups were traced. If recorded outside of our hospital, the ECGs were requested and sent to the investigators. Electrocardiograms were received from 15 hospitals, 15 health centers, and 1 private medical practice.

Electrocardiograms were classified for analysis if there was a mark confirming symptoms during the recording or if exact timing of recording during pain was clearly stated in the medical records. In the case of > 1 ECG recorded during pain, the ECG with maximal ischemic changes was chosen for analysis.

All ECGs were analyzed by 2 investigators (KN, ME) who were blinded to the clinical data. Right and left bundle branch block were defined by standard criteria.[17] Nonspecific intraventricular conduction block was defined as QRS duration of > 120 ms in the absence of typical bundle branch block or pacemaker ECG. Left ventricular hypertrophy was defined according to the Sokolow-Lyon criteria.[18] Our definition of circumferential subendocardial ischemia (global ischemia ECG pattern) was: ST-segment depression ≥ 0.5 mm in ≥ 6 leads, maximally in leads V_4–V_5 with inverted T waves, and ST-segment elevation ≥ 0.5 mm in lead aVR (Figure 1A, B). The ECG diagnosis of global ischemia was based solely on the actual qualifying ECG. No comparison with previous ECGs was conducted.

The ST segment, determined by drawing a line between subsequent TP segments, and measured 0.06 s after the J point, was considered elevated or depressed if it was ≥ 0.5 mm above or below the isoelectric line, respectively. The T wave was considered positive or negative if it was ≥ 1 mm above or below the isoelectric line, measured > 120 ms after the J point with the aid of a hand-held magnifying lens.

Table 1. Number of Patients and Reasons for Study Exclusion

Exclusion Criteria	LM+ Group, n	LM– Group, n
No ECG during pain	31	53
Left ventricular hypertrophy	4	2
Q waves or QRS > 120 ms[a]	18	11
Pacemaker ECG	0	2
Redo operation	4	0

[a]Includes right and left bundle branch block and nonspecific intraventricular conduction block.

Abbreviations: ECG, electrocardiogram; LM+, patients with left main coronary artery disease; LM– patients without left main coronary artery disease.

Statistical Analysis

Categorical variables were expressed as numbers of patients or percentages, and continuous variables were expressed as medians followed by interquartile range. We used the Chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney test for numerical variables. A 2-tailed P value of < 0.05 was considered statistically significant. Confidence intervals (CIs) were calculated at the 95% significance level. Comparison between the study and control groups was made using the log-rank test. Hazard ratios (HRs) were calculated by Cox regression analysis. Age, gender, and history of stroke, diabetes, hypertension, and smoking were included in the multivariate Cox regression model. All calculations were performed with the SPSS 16.0 statistical package (SPSS, Inc., Chicago, IL).

Results

Table 2 presents the baseline characteristics of the groups. No significant differences were found. In the LM+ group, 28 (35%) patients had unstable angina, 43 (54%) had non–ST-segment elevation myocardial infarction (MI), and 7 (9%) had ST-segment elevation MI. Two patients did not have ACS. In the LM– group, the corresponding numbers were 27 (42%), 27 (42%), and 11 (17%) patients, respectively. All of the patients in the LM- group had ACS. In the patients with MI, a final diagnosis of Q-wave MI was established in 6 and 8 patients in the LM+ and LM– groups, respectively. In the LM– group, 7 (11%) patients had 1-vessel disease, 11 (17%) had 2-vessel disease, and 47 (72%) had 3-vessel disease.

The distribution of ECG changes during anginal pain is presented in Table 3. The global ischemia ECG pattern was found in 61 (76%) of 80 patients with LM coronary artery disease and in 12 (19%) of 65 patients without LM coronary artery disease. The most frequent ECG presentation in LM– patients was ST-segment depression with positive T waves (Figure 2A, B).

The prespecified global ischemia ECG pattern criteria for LM stem stenosis had a sensitivity of 76% and a specificity of 81% to predict the angiography findings. In addition, the positive and negative predictive values were high, at 84% and 74%, respectively.

In multivariate analysis (Table 4), the global ischemia ECG pattern was strongly associated with angiographic

Table 2. Baseline Characteristics in Patients with and without Left Main Coronary Artery Disease

Baseline Characteristics[a]	LM+ Group n = 80 n (%)	LM– Group n = 65 n (%)	*P* Value
Age, years	70 (62–75)	67 (59–73)	0.17
Gender, male	46 (58)	42 (65)	0.40
Hypertension	46 (58)	39 (60)	0.87
Diabetes	16 (20)	9 (14)	0.38
Smoker	15 (19)	16 (25)	0.42
History of stroke	7 (9)	4 (6)	0.76
Medical treatment			
Aspirin	67 (84)	57 (88)	0.64
β-blockers	76 (95)	64 (99)	0.38
ACE inhibitors	26 (33)	23 (35)	0.73
Calcium antagonists	17 (21)	13 (20)	1.00
Digitalis	7 (9)	2 (3)	0.19
Nitrates	72 (90)	58 (89)	1.00
Diuretics	32 (40)	19 (29)	0.22
Lipid-lowering agents	53 (66)	75 (49)	0.27
Warfarin	6 (8)	3 (5)	0.73

[a]Variables are given as median values followed by interquartile ranges.
Abbreviations: ACE, angiotensin-converting enzyme; LM+, patients with left main coronary artery disease; LM–, patients without left main coronary artery disease.

LM coronary artery disease after adjusting for age, gender, stroke, diabetes, hypertension, and smoking (HR, 16.0; 95% CI, 6.5–39.5; $P < 0.001$).

Discussion

We found that 3 of 4 patients with LM coronary artery disease who had urgent or emergent CABG presented the global ischemia ECG pattern during anginal episodes. Less than 1 of 5 patients without LM coronary artery disease showed this ECG pattern. The difference is striking, considering that the LM– group also had severe coronary artery disease. Almost three-fourths of the control patients had 3-vessel disease. The difference is not explained by differences in patients' clinical presentations. There were only small differences between the groups with respect to ACS category.

Table 3. Distribution of ECG Changes During Anginal Pain in Patients with and without Left Main Coronary Artery Disease

ECG Pattern	LM+ Group n (%)	LM– Group n (%)
Global ischemia	61 (76)	12 (19)
Other ST-segment depression	7 (9)	28 (43)
Isolated T-wave changes	1 (1)	10 (15)
ST-segment elevation	9 (12)	13 (20)
Within normal limits	2 (2)	2 (3)

Abbreviations: ECG, electrocardiogram; LM+, patients with left main coronary artery disease; LM-, patients without left main coronary artery disease.

This study adds new, interesting data about this distinct ECG finding, which has only been studied in small patient groups. Sclarovsky et al[12] introduced the concept of T-wave inversion in combination with lateral ST-segment depression as a risk marker in ACS without ST-segment elevation. They studied 32 consecutive patients who had horizontal or downward-sloping ST-segment depression with peaked (n = 21) or inverted (n = 11) T waves. In the group with inverted T waves, the in-hospital mortality was 27%, whereas none of the patients with positive T waves died in the hospital. In addition, 7 of 10 patients with inverted T waves had significant LM coronary artery disease on angiography, while 2 of 10 patients had 3-vessel disease.

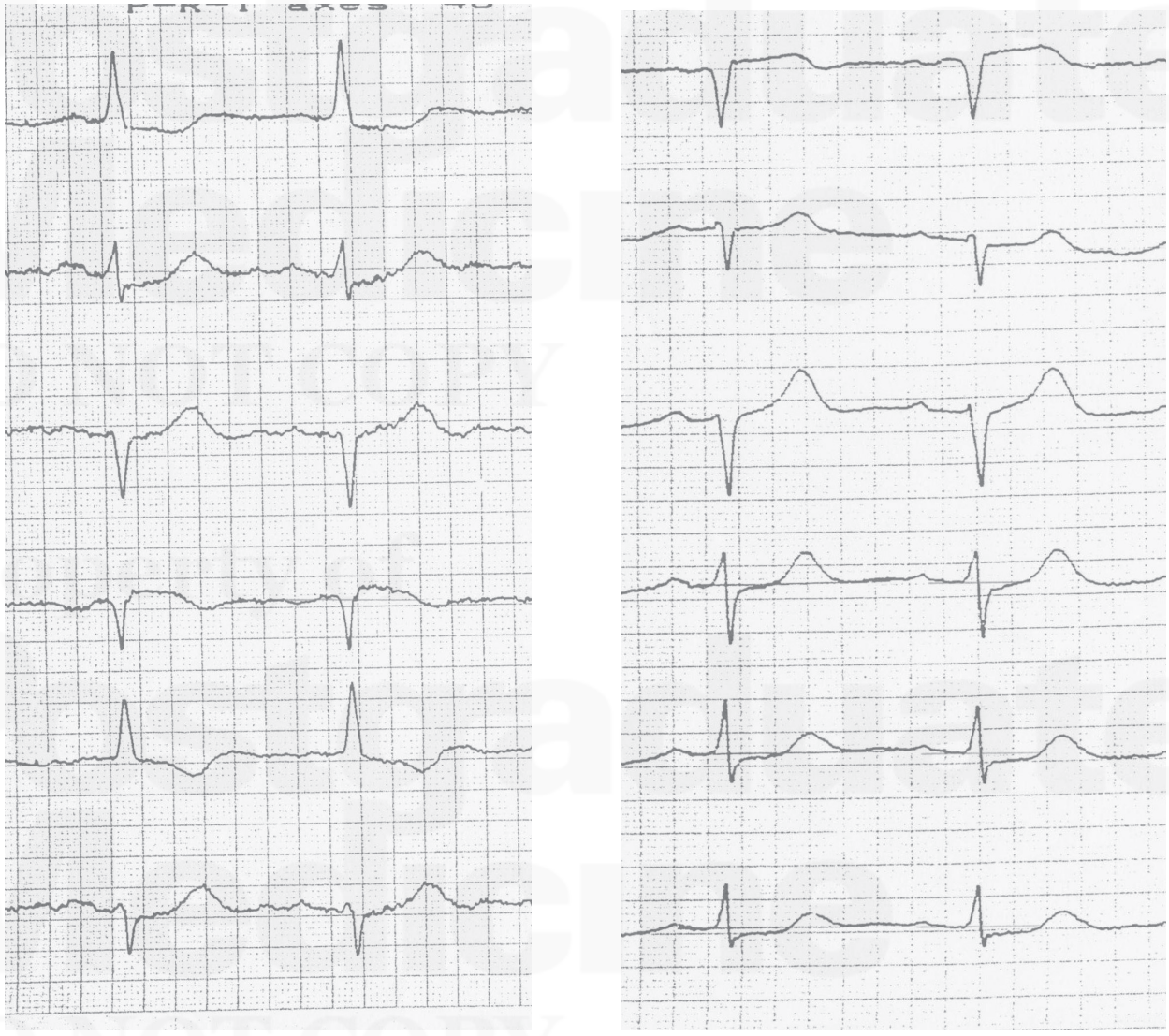
We reported earlier that patients (n = 25) with transient ST-segment depression and an inverted T wave maximally in leads V_4–V_5 during anginal pain had higher in-hospital mortality (24%) than patients with ST-segment depression and a positive T wave (0%).[14] Three-fourths of the patients with ST-segment depression and inverted T waves had LM coronary artery disease or LM coronary artery-equivalent disease on angiography, and one-fourth had severe 3-vessel disease. In the present study, no comparison with previous ECGs was conducted, but, typically, the ST-segment/T-wave changes were either new or represented accentuation of preexisting ST-segment/T-wave changes.

Barrabés et al[5] reported that the presence, magnitude, and extent of ST-segment depression were associated with increased mortality in patients with non–ST-segment elevation MI. ST-segment depression in ≥ 2 lateral (I, aVL, V_5, or V_6) leads proved to be the only ECG variable that predicted death after adjusting for baseline predictors. Patients with lateral ST-segment depression had higher mortality and severe heart failure rates than the remaining patients, although they had similar enzyme levels. In contrast, ST-segment depression not involving the lateral leads did not predict poor outcome. The authors did not include T waves in their analyses. One could speculate that the poor outcome in patients with lateral ST-segment depression was associated with circumferential subendocardial ischemia.

Atar et al[1] correlated 1-year mortality with location of ST-segment depression (leads I and aVL; II, III, and aVF; V_1–V_3; or V_4–V_6) and T-wave polarity in a retrospective analysis of the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB trial. They found that patients with ST-segment depression and T-wave inversion in leads V_4–V_6 had the highest 1-year mortality rate of all groups,

Figure 2A. Extremity leads I, II, III, aVR, aVL, and aVF.

Figure 2B. Precordial leads V_1–V_6.



Electrocardiogram (50 mm/sec) recorded during anginal pain in a patient with 3-vessel disease shows ST-segment depression in leads I, II, aVL, and V_4–V_6 with positive T waves in leads V_4–V_6. The ST segment is elevated in leads aVR and V_1.

significantly higher compared with patients with ST-segment depression without T-wave inversion in those leads. Logistic regression analysis revealed ST-segment depression with T-wave inversion in leads V_4–V_6 among a number of other independent predictors of 1-year mortality. Conversely, ST-segment depression without T-wave inversion in leads V_4–V_6 or other ECG presentations were not independent predictors of high 1-year mortality. These results support our findings.

We believe that the differences in prevalence of the global ischemia ECG pattern between the 2 groups are explained by more severe and extensive myocardial ischemia in the LM+ than in the LM– group patients. The exact electro-/pathophysiologic mechanisms of the global ischemia ECG pattern are not known. When myocardial ischemia is confined primarily to the subendocardium, the overall ST-segment vector typically faces the inner ventricular layer and the ventricular cavity, such that the surface ECG leads show ST-segment depression.[19] This subendocardial ischemic pattern is a frequent finding during spontaneous episodes of angina at rest and represents the typical ECG finding during exercise tests, as energy demands are highest and blood supply most precarious in the inner layers of the myocardium.[6] In these cases, extensive ischemia impairs relaxation of the left ventricle, resulting in increase of the

Table 4. Variables in the Multivariable Cox Proportional Hazards Model Examining the Probability of Left Main Coronary Artery Disease on Coronary Angiography

	Hazard Ratio	95% CI	*P* Value
Age	0.971	0.922–1.022	0.260
Global ischemia ECG pattern	16.021	6.503–39.472	< 0.001
Female gender	0.934	0.400–2.324	0.934
Smoking	1.699	0.570–5.065	0.341
History of stroke	1.263	0.220–7.252	0.793
Diabetes	1.164	0.391–3.465	0.785

Abbreviations: CI, confidence interval; ECG, electrocardiogram.

left ventricular end-diastolic pressure.[20] Inducing global left ventricular ischemia in dogs by hydraulic constriction of the LM resulted in a significant decrease in the endocardial-to-epicardial flow ratio and a significant increase in left ventricular end-diastolic pressure.[21] Additionally, inducing elevation of the left ventricular end-diastolic pressure by pacing in patients with significant coronary artery disease was associated with ST-segment depression in the ECG.[22] Hence, we speculate that the global ischemia ECG represents the electrical effects of severe subendocardial ischemia, which generates an ST-segment vector that points away from the apical/lateral leads V_4–V_5 and toward lead aVR.

To our knowledge, no previous studies have analyzed the prevalence of different ECG patterns during anginal symptoms in patients before CABG. These proportions would also be significantly affected by differences in criteria for choosing revascularization strategy between percutaneous coronary intervention and CABG. We decided to choose patients who underwent CABG urgently or emergently to test the diagnostic power of the global ischemia ECG pattern in patients with severe LM coronary artery disease. Silent or symptomatic ischemia is frequent in these patient categories. In high-risk patients undergoing noncardiac surgery or CABG, myocardial ischemia on 2-lead ambulatory monitoring or continuous 12-lead (ie, modified treadmill) monitoring were frequent, clinically silent, and usually independent of changes in myocardial oxygen demand.[23] The situation is probably different in stable angina pectoris. Using Holter monitoring, Jánosi et al[24] found silent ischemia in only 12.6% of 95 patients with stable angina pectoris during their stay in the surgery ward before CABG.

The present and aforementioned studies reveal that different manifestations of ST-segment/T-wave changes have significantly different prognostic implications. Still, in the modern era of high technology, the ECG has a central role in clinical decision making in ACS. We believe that much is to be gained by extending the ECG analysis beyond ST-segment elevation and non–ST-segment elevation categories.

Limitations

There are quite a few limitations to be reported in this study. First, the study population represents only a limited proportion of the original study population. This was primarily due to strict inclusion and exclusion criteria. Our results may not be applicable to patients with ECG confounders, such as left ventricular hypertrophy or pathological Q waves. On the other hand, all patients had coronary angiography, which enabled a correlation between the ECG findings and this gold standard in all patients. The study was a retrospective substudy, but the authors do not consider this a major limitation because the study objective was to compare ECG with angiographic findings.

Not all patients had a clinical diagnosis of ACS. However, all patients had urgent or emergent CABG, indicating severe LM coronary artery disease. Another possible limitation is the difference between the 2 patients groups concerning the number of patients excluded due to absence of ECG recorded during pain. Only patients who had isolated CABG were included in this study. Future studies should address the predictive power of the global ischemia ECG pattern with respect to severe LM coronary artery disease in different patient cohorts undergoing coronary angiography, as well as in patients not undergoing CABG.

Conclusion

We have identified a high-risk ECG pattern that differentiated patients with LM coronary artery disease from those without in patients who underwent isolated urgent or emergent CABG. The ECG pattern with widespread ST-segment depression maximally in leads V_4–V_5 with inverted T waves also known as the global ischemia ECG pattern, proved to be strongly correlated with angiographic LM coronary artery disease in multivariate analysis. From a therapeutic point of view, this study justifies the conclusion that future studies are needed to test whether urgent patient cases with ECG signs of LM coronary artery disease should have coronary angiography on an emergency basis.

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Conflict of Interest Statement

Kjell Nikus, MD, Otso Järvinen, MD, Samuel Sclarovsky, MD, Heini Huhtala, MSc, Matti Tarkka, MD, and Markku Eskola, MD disclose no conflicts of interest.

References

1. Atar S, Fu Y, Wagner GS, Rosanio S, Barbagelata A, Birnbaum Y. Usefulness of ST depression with T-wave inversion in leads V(4) to V(6) for predicting one-year mortality in non–ST-elevation acute coronary syndrome (from the Electrocardiographic Analysis of the Global Use of Strategies to Open Occluded Coronary Arteries IIB Trial). *Am J Cardiol*. 2007;99(7):934–938.
2. Cannon CP, McCabe CH, Stone PH, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. Thrombolysis in Myocardial Ischemia. *J Am Coll Cardiol*. 1997;30(1):133–140.
3. Miller WL, Sgura FA, Kopecky SL, et al. Characteristics of presenting electrocardiograms of acute myocardial infarction from a community-based population predict short- and long-term mortality. *Am J Cardiol*. 2001;87(9):1045–1050.
4. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA*. 1999;281(8):707–713.
5. Barrabés JA, Figueras J, Moure C, Cortadellas J, Soler-Soler J. Prognostic significance of ST segment depression in lateral leads I, aVL, V5 and V6 on the admission electrocardiogram in patients with a first acute myocardial infarction without ST segment elevation. *J Am Coll Cardiol*. 2000;35(7):1813–1819.
6. Nikus K, Pahlm O, Wagner G, et al. Electrocardiographic classification of acute coronary syndromes: a review by a committee of the International Society For Holter And Non-Invasive Electrocardiology. *J Electrocardiol*. 2010;43(2):91–103.
7. Caracciolo EA, Davis KB, Sopko G, et al. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. *Circulation*. 1995;91(9):2335–2344.
8. Kaul P, Fu Y, Chang WC, et al; PARAGON-A and GUSTO IIb Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network. Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. PARAGON-A and GUSTO IIb Investigators. Platelet IIb/IIIa Antagonism for the Reduction of Acute Global Organization Network. *J Am Coll Cardiol*. 2001;38(1):64–71.
9. Holmvang L, Clemmensen P, Lindahl B, et al. Quantitative analysis of the admission electrocardiogram identifies patients with unstable coronary artery disease who benefit the most from early invasive treatment. *J Am Coll Cardiol*. 2003;41(6):905–915.
10. Savonitto S, Cohen MG, Politi A, et al. Extent of ST-segment depression and cardiac events in non–ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2005;26(20):2106–2113.
11. Barrabés JA, Figueras J, Moure C, Cortadellas J, Soler-Soler J. Prognostic value of lead aVR in patients with a first non–ST-segment elevation acute myocardial infarction. *Circulation*. 2003;108(7):814–819.
12. Sclarovsky S, Rechavia E, Strasberg B, et al. Unstable angina: ST segment depression with positive versus negative T wave deflections—clinical course, ECG evolution, and angiographic correlation. *Am Heart J*. 1988;116(4):933–941.
13. Nikus KC, Eskola MJ. The ECG in a mechanical obstruction of the ostium of the left main coronary artery. *Int J Cardiol*. 2002;86(2–3):327–329.
14. Nikus KC, Eskola MJ, Virtanen VK, et al. ST-depression with negative T waves in leads V4-V5—a marker of severe coronary artery disease in non-ST elevation acute coronary syndrome: a prospective study of angina at rest, with troponin, clinical, electrocardiographic, and angiographic correlation. *Ann Noninvasive Electrocardiol*. 2004;9(3):207–214.
15. Sclarovsky S. Angina at rest and acute myocardial ischemia. In: *Electrocardiography of Acute Myocardial Ischaemic Syndromes*. London, UK: Martin Dunitz Ltd; 1999:1–29.
16. Järvinen O, Huhtala H, Laurikka J, Tarkka MR. Higher age predicts adverse outcome and readmission after coronary artery bypass grafting. *World J Surg*. 2003;27(12):1317–1322.
17. Willems JL, Robles de Medina EO, Bernard R, et al. Criteria for intraventricular conduction disturbances and pre-excitation. World Health Organizational/International Society and Federation for Cardiology Rask Force Ad Hoc. *J Am Coll Cardiol*. 1985;5(6):1261–1275.
18. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J*. 1949;37(2):161–186.
19. Cook RW, Edwards JE, Pruitt RD. Electrocardiographic changes in acute subendocardial infarction. I. Large subendocardial and large nontransmural infarcts. *Circulation*. 1958;18(4 part 1):603–612.
20. Grossman W. Evaluation of systolic and diastolic function of the ventricles and myocardium. In: Baim DS, Grossman W, eds. *Grossman's Cardiac Catheterization, Angiography, and Intervention*. 6th ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2001:367–390.
21. Visner MS, Arentzen CE, Parrish DG, et al. Effects of global ischemia on the diastolic properties of the left ventricle in the conscious dog. *Circulation*. 1985;71(3):610–619.
22. Aroesty JM, McKay RG, Heller GV, Royal HD, Als AV, Grossman W. Simultaneous assessment of left ventricular systolic and diastolic dysfunction during pacing-induced ischemia. *Circulation*. 1985; 71(5):889–900.
23. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med*. 1990;323(26):1781–1788.
24. Jánosi A, Hankóczy J, Vértes A, Kádár A, Fehér A, Arvay A. Preoperative silent myocardial ischemia. Has it prognostic significance? *Cardiology*. 1991;78(2):95–98.