Tampere University

KIMMO KOIVULA

Electrocardiogram in Assessing Mortality in Acute Coronary Syndromes

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine and Health Technology
of Tampere University,
for public discussion in the Auditorium 1 (Ruori building)
of South Karelia Central Hospital, Valto Käkelän katu 3, Lappeenranta,
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ACADEMIC DISSERTATION
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Responsible supervisor	Docent Markku Eskola Tampere University Finland	
Supervisors	Professor (emeritus) Kjell Nikus Tampere University Finland	M.D., Ph.D. Jyrki Lilleberg University of Helsinki Finland
Pre-examiners	Docent Aapo Aro University of Helsinki Finland	M.D., Ph.D. Kari Kaikkonen University of Oulu Finland
Opponent	Professor Juhani Junttila University of Oulu Finland	
Custos	Professor (emeritus) Kjell Nikus Tampere University Finland	

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ABSTRACT

The electrocardiogram (ECG) has been the cornerstone of diagnosing acute myocardial infarction for over hundred years. Studies have shown that in acute coronary syndromes (ACS), ECG can be used to assess the prognosis of patients. The role of ECG in assessing the outcome of real-life ACS patients is not well known.

This thesis comprises three studies (referred to as Study I, II, and III). We studied patients suffering from ACS. They were divided into groups according to the ECG changes. The main aims of the study were to explore the patient characteristics and outcome within the ECG groups in unselected real-life cohorts. In Study I, we investigated the mid-term mortality of ST-elevation myocardial infarction (STEMI) patients with grade 2 (G2I) and grade 3 ischemia (G3I). We also included STEMI patients to whom ischemia grading does not apply (No grade, NG). In Study II, we studied the impact of Q waves and/or T-wave inversion (TWI) on the mortality of STEMI patients. The patients were categorized based on the presence (Q+, TWI+) or absence (Q-, TWI-) of these ECG parameters. In Study III, we investigated the impact of different ECG changes on the long-term mortality of ACS patients.

In Studies I and II, we used the combined data of the HUS-STEMI (n=448) and STEMI 2005 (n=310) studies. These studies were observational, and consecutive STEMI patients were enrolled. Study III was based on the data of the TACOS study (n=1184), in which consecutive patients with confirmed ACS were enrolled. Mortality data were gathered from the national database (Statistics Finland).

In Study I, 30-day mortality was 6.8% in G2I, 14.8% in G3I, and 15.3% in NG, $p=0.003$. One-year mortality was 10.3%, 18.6%, and 25.2% in the respective groups, $p<0.001$. In the logistic regression univariate analysis, patients with G3I (OR 2.00, 95% CI 1.07-3.72) and NG (OR 2.95, 95% CI 1.79-4.84) had higher risk of death at one year compared to those with G2I. In the multivariable model, NG predicted one-year mortality (OR 2.82, 95% CI 1.79-4.84), but G3I had no statistically significant effect on one-year mortality (OR 2.36, 95% CI 0.924-6.03).

In Study II, Q waves and TWI were found to be associated with the one-year mortality of STEMI patients. Mortality was highest in patients with both Q waves and TWI (31.0%): one-year mortality was 22.0% in Q-TWI+, 19.2% in Q+TWI-, and 9.8% in STEMI patients with none of these changes, p=0.002. In the logistic regression univariate analysis, all three groups with Q waves and/or TWI (Q+TWI+, Q+TWI- and Q-TWI+) predicted one-year mortality statistically significantly compared to Q-TWI-. In the multivariable analysis, Q+TWI+ independently predicted one-year mortality (OR 7.14, 95% CI 2.05-24.9), while the results in the other two groups lacked statistical significance.

The most important finding of Study III was that the pre-specified ECG findings affected long-term mortality in ACS differently. The Kaplan-Meier analysis showed the best survival in patients with a normal ECG. Survival worsened in the following order: ST elevation, ST depression/TWI, right bundle branch block (RBBB), Q wave, other ECG change, global ischemia, left ventricular hypertrophy (LVH), and left bundle branch block (LBBB), p<0.001. When adjusted for age and gender, LBBB (HR 3.25, 95% CI 1.65-6.40, p=0.001), other ECG change (HR 3.01, 95% CI 1.56-6.09, p=0.001), LVH (HR 2.54, 95% CI 1.29-4.97, p=0.007), Q waves (HR 2.28, 95% CI 1.20-4.32, p=0.012), and global ischemia (HR 2.22, 95% CI 1.14-4.31, p=0.019) were statistically significantly associated with 10-year mortality. RBBB, ST elevation, and ST depression/TWI had no statistically significant effect on 10-year mortality.

Conclusion. The ECG can be used to predict mortality in STEMI and other ACSs. G3I predicts higher mortality than G2I, but the highest mortality rate was found in patients for whom ischemia grading does not apply. Q waves and TWI increase the risk of death in STEMI, and mid-term mortality is highest in STEMI patients with both Q waves and TWI in their presenting ECG. Long-term outcomes of ACS can be predicted using ECG; patients with LBBB have the highest mortality rate.

TIIVISTELMÄ

Sydänsähkökäyrä eli EKG on ollut sydäninfarktin diagnosoinnin kulmakivi yli sadan vuoden ajan. Aikaisemmat tutkimukset ovat osoittaneet, että EKG:ssä nähtävien muutosten avulla voidaan arvioida sepelvaltimotautikohtauksen saaneen potilaan ennustetta. EKG:n merkitystä tosielämän sepelvaltimokohtauspotilaiden ennusteen arvioinnissa ei tunneta hyvin.

Tämä väitöskirja koostuu kolmesta osatutkimuksesta (tutkimus I, II ja III). Tutkimme sepelvaltimotautikohtauksen saaneita potilaita ja jaoimme heidät ryhmiin EKG:ssä todettujen muutosten perusteella. Tavoitteena oli tutkia valikoimattomassa tosielämän potilasjoukossa, miten EKG:n perusteella jaetut potilasryhmät eroavat toisistaan riskitekijöiden ja taustasairauksien suhteen. Lisäksi tutkimme EKG-muutosten merkitystä ennusteeseen. Tutkimuksessa I selvitimme, mikä on keskipitkän aikavälin kuolleisuus potilailla, joilla on ST-nousuinfarkti (ST-elevation myocardial infarction; STEMI) ja EKG:n perusteella iskemia-asteluokka 2 (Grade of ischemia 2; G2I) tai 3 (Grade of ischemia 3; G3I). Selvitimme myös niiden STEMI-potilaiden kuolleisuutta, joihin ei voida soveltaa iskemia-asteluokittelua (ryhmä ”no grade”; NG). Tutkimuksessa II selvitimme Q-aallon ja T-aallon inversion vaikutusta yhdessä ja erikseen STEMI-potilaiden kuolleisuuteen. Tutkimuksessa III selvitimme, mikä on eri EKG-muutosten merkitys sepelvaltimotautikohtauksen pitkän aikavälin kuolleisuuteen.

Tutkimusten I ja II aineistona käytettiin HUS-STEMI- (n=448) ja STEMI 2005 -tutkimuksen (n=310) yhdistettyä potilasaineistoa. Kumpikin tutkimus oli havainnoiva, ja niihin otettiin peräkkäisiä STEMI-potilaita. Tutkimuksen III aineistona käytettiin TACOS-tutkimuksen (n=1184) potilaita. TACOS-tutkimukseen otettiin peräkkäisiä potilaita, joilla oli varmennettu sepelvaltimotautikohtaus. Kuolleisuustiedot saatiin Suomen kansallisesta kuolinsyyrekisteristä.

Tutkimuksessa I todettiin, että kuukauden kuolleisuus oli G2I-potilailla 6,8 %, G3I-potilailla 14,8 % ja NG-potilailla 15,3 %, p=0,003. Vuoden kuolleisuus näillä ryhmillä oli 10,3 %, 18,6 % ja 25,2 %, p<0,001. Logistisen regression yhden

muuttujan analyysissa G3I-potilailla (OR 2,00, 95 % CI 1,07–3,72) ja NG-potilailla (OR 2,95, 95 % CI 1,79–4,84) oli korkeampi riski kuolla vuoden kuluessa kuin G2I-potilailla. Monimuuttujamallissa NG ennusti vuoden kuolleisuutta (OR 2,82, 95 % CI 1,79–4,84), mutta G3I ei ennustanut vuoden kuolleisuutta tilastollisesti merkitsevästi (OR 2,36, 95 % CI 0,924–6,03).

Tutkimuksessa II todettiin, että Q-aallot ja T-inversiot diagnoosivaiheen EKG:ssä liittyivät STEMI-potilaan vuoden kuolleisuuteen, ja korkein kuolleisuus on potilailla, joilla on sekä Q-aalto että T-inversio (Q+TWI+) (31,0 %). T-inversio ilman Q-aaltoa (Q-TWI+) johti 22,0 % kuolleisuuteen, ja Q-aalto ilman T-inversiota (Q+TWI-) 19,2 % kuolleisuuteen. Ilman kumpaakin EKG-muutosta (Q-TWI-) kuolleisuus oli 9,8 %, p=0,002. Logistisen regression yhden muuttujan analyysissa kukin ryhmä ennusti vuoden kuolleisuutta tilastollisesti merkitsevästi verrattuna Q-TWI- -ryhmään. Monimuuttuja-analyysissa ainoastaan Q+TWI+ ennusti itsenäisesti vuoden kuolleisuutta (OR 7,14, 95 % CI 2,05–24,9), kun taas muiden ryhmien ennustevaikutus ei ollut tilastollisesti merkitsevä.

Tutkimuksen III tärkein havainto oli, että eri EKG-löydöksillä on erilainen kuolleisuusvaikutus pitkällä aikavälillä sepelvaltimotautikohtaukseen sairastuneilla potilailla. Kaplan-Meier-analyysi näytti, että paras ennuste on potilailla, joiden EKG on normaali. Ennuste huononi seuraavassa järjestyksessä eri EKG-muuttujilla: ST-nousu, ST-lasku tai T-inversio, oikea haarakatkos, Q-aalto, muu EKG-muutos, globaali iskemia, vasemman kammion hypertrofia ja vasen haarakatkos, p<0,001. Iällä ja sukupuolella vakioituna kuolleisuutta kymmenen vuoden seurannassa ennustivat vasen haarakatkos (HR 3,25, 95 % CI 1,65–6,40, p=0,001), muut EKG-muutokset (HR 3,01, 95 % CI 1,56–6,09, p=0,001), vasemman kammion hypertrofia (HR 2,54, 95 % CI 1,29–4,97, p=0,007), Q-aallot (HR 2,28, 95 % CI 1,20–4,32, p=0,012) sekä globaali iskemia (HR 2,22, 95 % CI 1,14–4,31, p=0,019). Oikea haarakatkos, ST-nousu tai ST-lasku/T-inversio eivät ennustaneet kymmenen vuoden kuolleisuutta tilastollisesti merkitsevästi.

Johtopäätökset. Kuolleisuutta voidaan ennustaa EKG:n perusteella STEMI:ssä ja muissa sepelvaltimotautikohtaustyypeissä. G3I ennustaa korkeampaa kuolleisuutta kuin G2I, mutta suurin kuolleisuus on potilailla, joihin tämä luokittelu ei päde. Q-aallot ja T-inversiot lisäävät kuoleman riskiä STEMI-potilailla, ja suurin kuolleisuus on niillä, joilla on sekä Q-aalto että T-inversio tulovaiheen EKG:ssä. Sepelvaltimotautikohtauksen pitkän aikavälin ennustetta voidaan arvioida EKG:n perusteella, ja korkein kuolleisuus on potilailla, joilla on vasen haarakatkos.

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ABBREVIATIONS

ACEi	Angiotensin converting enzyme inhibitor
ACO	Acute coronary occlusion
ACS	Acute coronary syndrome
AIVR	Accelerated idioventricular rhythm
AMI	Acute myocardial infarction
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid
ASSENT (trial)	The ASsessment of Safety and Efficacy of a New Treatment strategy with percutaneous coronary intervention, a series of trials
AW	Anderson-Wilkins (acuteness score)
BBB	Bundle branch block
CABG	Coronary artery bypass graft
CCB	Calcium channel blocker
CHF	Congestive heart failure
CI	Confidence interval
CMR	Cardiac magnetic resonance (imaging)
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
cTn	Cardiac troponin
CV	Cardiovascular
DANAMI (trial)	The DANish trial in Acute Myocardial Infarction
ECG	Electrocardiogram
ECG-LVH	Left ventricular hypertrophy assessed with ECG
EMI	Evolving myocardial infarction
ESC	European Society of Cardiology
FT	Fibrinolytic therapy
FTT	Fibrinolytic Therapy Trialists´ Collaborative Group
fQRS	Fragmented QRS
G2I	Grade 2 ischemia

G3I	Grade 3 ischemia
GI	Global ischemia
GRACE	The Global Registry of Acute Coronary Events
GREAT (trial)	The Grampian Region Early Anistreplase Trial
GUSTO (trial)	Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries, a series of clinical trials
HR	Hazard ratio
IQR	Interquartile range
IRA	Infarct-related artery
IVCD	Intraventricular conduction delay
LAD	Left anterior descending coronary artery
LAHB	Left anterior hemiblock
LBBB	Left bundle branch block
LCx	Left circumflex coronary artery
LM	Left main coronary artery
LV	Left ventricle
LVH	Left ventricular hypertrophy
MACE	Major adverse cardiac events
MI	Myocardial infarction
NG	No grade of ischemia
NRT	No reperfusion therapy
NSTE-ACS	Non-ST-elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
NYHA	New York Heart Association
ON-TIME (trial)	ONgoing Tirofiban In Myocardial infarction Evaluation, a series of trials
OR	Odds ratio
PCI	Percutaneous coronary intervention
PET-CT	Positron emission tomography/computed tomography
PIS	Pre-infarction syndrome
pPCI	Primary percutaneous coronary intervention
PURSUIT (trial)	Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy
RBBB	Right bundle branch block
RR	Risk ratio

RCA	Right coronary artery
SPECT	Single-photon emission computed tomography
STD	ST depression
STE	ST elevation
STEMI	ST elevation myocardial infarction
STR	ST resolution
STREAM (trial)	STrategic Reperfusion Early After Myocardial infarction, trial
TACOS	Tampere Acute COronary Syndrome study
TIA	Transient ischemic attack
TIMI (flow)	Thrombolysis In Myocardial Infarction. Angiographic measure of coronary flow (TIMI 0-3). TIMI 0 means no flow, and TIMI 3 means normal flow.
TIMI (trial)	Thrombolysis In Myocardial Infarction. A study group and series of clinical trials.
TOTAL (trial)	ThrOmbecTomy with PCI or PCI ALone
TWI	T-wave inversion
UA	Unstable angina

LIST OF ORIGINAL PUBLICATIONS

Publication I Koivula K, Eskola M, Viikilä J, Lilleberg J, Huhtala H, Birnbaum Y, Nikus K. Outcome of all-comers with STEMI based on the grade of ischemia in the presenting ECG. J Electrocardiol. 2018 Jul-Aug;51(4):598-606. doi: 10.1016/j.jelectrocard.2018.03.014. Epub 2018 Apr 4. PMID: 29996997.

Publication II Koivula K, Nikus K, Viikilä J, Lilleberg J, Huhtala H, Birnbaum Y, Eskola M. Comparison of the prognostic role of Q waves and inverted T waves in the presenting ECG of STEMI patients. Ann Noninvasive Electrocardiol. 2019 Jan;24(1):e12585. doi: 10.1111/anec.12585. Epub 2018 Sep 6. PMID: 30191632; PMCID: PMC6931455

Publication III Koivula Ka, Konttila KKa, Eskola MJ, Martiskainen M, Huhtala H, Virtanen VK, Mikkelsson J, Järvelä K, Niemelä KO, Karhunen PJ, Nikus KC. Long-term outcome of pre-specified ECG patterns in acute coronary syndrome. J Electrocardiol. 2020 Sep-Oct;62:178-183. doi: 10.1016/j.jelectrocard.2020.08.001. Epub 2020 Aug 8. PMID: 32950774

a Equal contributions

AUTHOR´S CONTRIBUTION

Publications I and II

The author took part in the design of the publications. In publication I, the decision to include patients with "no grade of ischemia" in the analyses was based on the author's suggestion, and it proved to be the main point of this publication. In both publications, the author analyzed all the ECGs and refined the analysis after comments from the experts in the research team. The author did all the statistical analyses with instructions from the statistician of the research team. The author wrote the articles and revised the text according to the feedback from the co-authors and created all the tables and figures. The author submitted the articles to the journals and was the main writer of the manuscript revisions and responses to the reviewers.

Publication III

The initial design and preliminary statistical analyses were done by Kaari Konttila. The author wrote the article and revised it according to the feedback from the co-authors. At that point, the research team decided to add right bundle branch block as a separate category (formerly, these patients were in the group "Other"), and the author re-analyzed all the ECGs in the group "Other" and in the group "LBBB." The author also went through all STEMI ECGs, and altogether, re-analyzed nearly half of the ECGs. After this, the author repeated all the statistical analyses using the revised ECG groups. The author did the analyses according to instructions from the statistician and according to the preliminary design. The author created all the tables and figures and submitted the manuscript to the journal. The author was the main writer of the manuscript revisions and responses to the reviewers.

1 INTRODUCTION

In 1920, Harold E.B. Pardee described the electrocardiogram (ECG) findings of a patient suffering from acute myocardial infarction (AMI) (Pardee, 1920). Since then, the ECG has become an important modality in assessing the outcome and choosing the treatment for patients with suspected acute coronary syndrome (ACS). The most fundamental question is whether the patient has ST elevation myocardial infarction (STEMI) or other ECG findings suggestive of acute coronary occlusion (ACO), or if the ECG predicts a non-occlusive state. STEMI and other ACOs require urgent treatment, and the European Society of Cardiology (ESC) recommends recording an ECG within 10 minutes of the first patient contact when there is a suspicion of ACS. (Collet et al., 2020)

The STEMI vs. non-ST-elevation myocardial infarction (NSTEMI) dichotomy replaced the previous Q-wave AMI vs. non-Q-AMI dichotomy after the Fibrinolytic Therapy Trialists´ Collaborative Group (FTT) in their large-scale meta-analysis, published in 1994, reported that patients with ST elevation or bundle branch block (BBB) benefited most from fibrinolytic therapy (FTT, 1994).

In STEMI, several ECG features can be used to assess outcome. Q waves (Siha et al., 2012), T-wave inversion (TWI) (Herz et al., 1999), and signs of evolving myocardial infarction (Q waves and/or TWI) (Eskola et al., 2007) are known to negatively affect outcome in STEMI, which is the case also for grade 3 ischemia (G3I) when compared with grade 2 ischemia (G2I) (Postma et al., 2011). However, there is little data on the real-life outcome of the grades of ischemia. The relevance of Q waves and TWI in assessing the outcome of STEMI separately and combined is not well-known.

Although previous studies have reported poor outcome of ST depression (Kaul et al., 2001) and relatively favorable outcome of TWI (Sarak et al., 2016) in non-ST-elevation ACS (NSTE-ACS), the prognostic aspects of different ECG findings, such as Q waves, right bundle branch block (RBBB), left bundle branch block (LBBB), or left ventricular hypertrophy (LVH) have been less studied.

2 REVIEW OF THE LITERATURE

2.1 Acute Coronary Syndromes

Acute coronary syndromes (ACS) comprise STEMI, NSTEMI, and unstable angina (UA). ACS is suspected in a patient with acute symptoms characteristic of myocardial ischemia, such as chest pain, chest discomfort or dyspnea. In STEMI, ischemic symptoms lasting for at least 20-30 minutes are accompanied by characteristic ECG findings. In NSTEMI, ST-segment and/or T-wave changes are typically present, but the ECG can be normal as well. In practice, ST elevation compatible with STEMI excludes NSTEMI. Elevated cardiac troponin (cTn) over the 99th percentile upper reference limit is essential for the diagnosis of STEMI and NSTEMI. In UA, the patient experiences chest pain or other symptoms indicating ACS (with or without ECG changes similar to NSTEMI), but no cardiac myocyte necrosis can be detected by laboratory tests — the cTn levels are not elevated. NSTEMI and UA constitute NSTE-ACS. (Collet et al., 2020; Ibanez et al., 2018)

The short- and long-term mortality of ACS is high. The highest long-term mortality was reported in NSTEMI and the lowest in UA (Ellis et al., 2019; K. C. Nikus et al., 2007). Treatment of ACS has improved over time and this may affect the outcome for patients (Gandhi et al., 2022). ACSs affect millions of people annually worldwide and inflict a heavy economic burden on societies (Reed, Rossi, & Cannon, 2017)

2.1.1 Pathophysiology of Acute Coronary Syndromes

The heart is normally perfused by the right (RCA) and left coronary artery. In the majority of individuals, the short left main coronary artery (LM) bifurcates into the left anterior descending (LAD) and the left circumflex coronary artery (LCx). The RCA normally perfuses the right ventricle (RV) and parts of the left ventricle (LV). The LAD perfuses the anterior and anteroapical areas of the LV, as well as the main part of the inter-ventricular septum, while the LCx perfuses the lateral areas. The

inferior wall is perfused by either the RCA or the LCx, the former (right dominance) being more common. (Pereztol-Valdes et al., 2005)

The myocardium is dependent on a constant flow of oxygen and nutrients via the coronary arteries. In ACS, there is an imbalance between oxygen supply and demand, which results in myocardial ischemia. The most common reason is rupture of an atherosclerotic plaque or coronary artery endothelial erosion. This is called type 1 myocardial infarction (MI) when it leads to myocardial necrosis. Breaking of the endothelium exposes the subendothelial structures to the coagulation system and leads to superimposed thrombus. Coronary thrombosis may cause partial or total obstruction of a coronary artery. (Collet et al., 2020; Thygesen et al., 2018)

Inflammation of coronary arteries is essential for thrombus formation, and without inflammation and other prothrombotic features, plaque ruptures may even go unnoticed as no obstructive thrombus is formed (Montecucco, Carbone, & Schindler, 2016).

In STEMI, there is typically total or subtotal occlusion of one of the main coronary arteries or their side branches or distal branches, resulting in transmural ischemia of the area perfused by the artery. In NSTEMI, total occlusion is less frequent, while multivessel disease is more frequent. (Abbott, Ahmed, Vlachos, Selzer, & Williams, 2007; Savonitto et al., 1999) Consequently, ischemia is often restricted to the subendocardial ventricular area in NSTEMI (Sarafoff et al., 2013). The pathophysiology of UA is similar to that of STEMI and NSTEMI, but ischemia is reversible and there is no detectable myocardial cell death (Collet et al., 2020).

ACS can also occur without plaque rupture or endothelial erosion in the coronary artery. Instead, factors such as hypotension, severe hypertension, anemia, hypoxemia, tachycardia, bradycardia, endothelial dysfunction, coronary spasm, or coronary artery dissection may cause an imbalance between oxygen supply and demand. Stable stenotic coronary artery plaques are often present in such cases, but ACS may evolve even without narrowing of the arterial lumen. If this kind of myocardial hypoperfusion leads to myocardial cell death and elevated cTn, the patient has suffered a type 2 MI. (Thygesen et al., 2018) ST elevation is rare in type 2 MI, and the typical presentation is NSTEMI (Saaby et al., 2014). Type 3 MI is defined as sudden cardiac death due to MI with no cTn values available. Type 4 MI is associated with percutaneous coronary intervention (PCI) and type 5 MI with coronary artery bypass grafting (CABG). Myocardial injury – presenting as elevated cTn – may take place in many different clinical conditions, including sepsis or heart

failure. Both myocardial injury and evidence of acute myocardial ischemia are required for the diagnosis of MI. (Thygesen et al., 2018)

Blood flow in the coronary arteries may be restored spontaneously or by reperfusion therapy. If reperfusion takes place swiftly, there may be little or no permanent damage in the myocardium. In dog models, ischemia of 20 minutes led to cell death and progressive necrosis (Jennings & Ganote, 1974). Certain factors have an impact on how susceptible the myocardium is to ischemic damage. Previous ischemia provides the myocardium with some protection against new episodes of prolonged ischemia. This phenomenon is called ischemic preconditioning (Iliodromitis, Lazou, & Kremastinos, 2007; Murry, Jennings, & Reimer, 1986). In addition, the affected myocardium may be protected by collateral flow from non-obstructed arteries (Meier et al., 2013).

2.1.2 Treatment of STEMI

Current guidelines emphasize quick restoration of coronary flow in STEMI, and this is preferably carried out by primary PCI (pPCI). In PCI, the preferred arterial route is the radial artery, and the coronary artery to be treated is imaged using X-ray and contrast injection. A guide wire inside a guiding catheter is inserted distal to the coronary artery stenosis and a balloon catheter is introduced along the wire and dilated (angioplasty). In practically all pPCI procedures, one or more drug-eluting stents are implanted. (Ibanez et al., 2018)

Fibrinolytic therapy (FT) is the alternative reperfusion therapy, when the estimated delay to the invasive procedure is >120 min or when PCI is not available. However, there are several contraindications to FT, because of the associated bleeding risk. Studies have shown that PCI results in better outcome than FT (Keeley, Boura, & Grines, 2003), but FT is still an acceptable choice in low-risk STEMI patients and in countries and regions with long distances and incomplete regional coverage of pPCI networks (Armstrong et al., 2013; Ibanez et al., 2018; Viikila et al., 2013).

Ancillary therapy in both PCI and FT includes double anti-platelet therapy and low-molecular weight heparin. Anti-platelet therapy consists of acetylsalicylic acid (ASA) combined with a $P2Y_{12}$ inhibitor. The preferred $P2Y_{12}$ inhibitors in PCI are ticagrelor and prasugrel. Clopidogrel is used in patients who receive FT. The choice and dosing of the medication also depends on patient comorbidities, other

medication, especially anticoagulation therapy, and patient age. After reperfusion therapy, high-dose statin, angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), and beta-blocker therapy is recommended for most STEMI patients. Mineralocorticoid receptor antagonists, mainly spironolactone, are used in the case of severely depressed left ventricular function. (Ibanez et al., 2018) Likewise, dapagliflozin/empagliflozin and sacubitril-valsartan belong to the modern treatment of heart failure after STEMI (McDonagh et al., 2021).

2.1.3 Prognosis of STEMI

According to a registry study, patient outcome of STEMI has improved considerably during the last few decades thanks to the introduction of modern reperfusion therapies (Puymirat et al., 2012). In a large prospective observational study conducted in the Netherlands, 30-day mortality was 17% and three-year mortality 27% in 1985-1990, when less than half of the patients received reperfusion therapy (either FT or PCI). In 2000-2008, when most of the patients were treated with PCI, 30-day mortality had dropped to 6% and three-year mortality to 13% (Nauta et al., 2011).

2.1.3.1 Short- and Long-term Mortality with Fibrinolytic Therapy

The first randomized controlled trials with FT showed improvement in LV function and reduction in short-term mortality with streptokinase or anistreplase (AIMS Trial Study Group, 1988; I.S.A.M. Study Group, 1986). With newer plasminogen activators as fibrinolytic agents, 30-day mortality was roughly 6% in a large multicenter study (ASSENT-2) (Van De Werf et al., 1999). Another large study (GUSTO V) with a plasminogen activator showed 30-day mortality rates of 5.6–5.9% (Topol & Investigators, 2001). In older studies, routine invasive evaluation was not performed. In the STREAM trial, FT-treated patients underwent routine angiography within 24 hours or immediately, if the FT failed; this resulted in a 30-day mortality of 4.6% (Armstrong et al., 2013). In a Swedish real-life registry study, 30-day mortality was 11.4% with in-hospital FT and 7.6% with pre-hospital FT, while the one-year mortality rates were 15.9% and 10.3%, respectively (Stenestrand, Lindback, Wallentin, & Registry, 2006).

In the ASSENT-2 trial, one-year mortality was 9.1-9.2% with no statistically significant difference between the two studied plasminogen activators (P. Sinnaeve et al., 2003). FT-treated and routinely invasively evaluated patients in the STREAM trial had a one-year mortality of 6.7% (P. R. Sinnaeve et al., 2014). The GREAT study showed a clear benefit of pre-hospital FT over in-hospital FT: the five-year mortality was 25% in the pre-hospital FT group and 36% in the in-hospital group (Rawles, 1997). A long-term follow-up of the GUSTO-I study showed 11-year mortality rates of 26.3-68.2% among the 30-day survivors depending on the patients' age and presence of initial cardiogenic shock. The overall 11-year mortality among patients who were alive 30 days post-MI was 31.2% (Singh et al., 2007).

2.1.3.2 Short- and Long-term Mortality with Primary PCI

The DANAMI-2 trial showed the overall superiority of pPCI over FT, although there was no difference in mortality alone. In the pPCI group, 30-day mortality was 6.6% and 7.8% in the FT group, p=0.35 (Andersen et al., 2003). An even lower 30-day all-cause mortality (2.0-3.3%) was seen in the ATLANTIC study (Gilles Montalescot et al., 2014). Swedish real-life registry data showed a 4.9% 30-day mortality and 7.6% one-year mortality in pPCI-treated patients (Stenestrand et al., 2006).

In the large TOTAL trial, one-year all-cause mortality after pPCI was 4.3-4.5% (Jolly et al., 2016). The long-term follow-up data of the DANAMI-2 trial showed an eight-year all-cause mortality rate of 27.3% (30.8% in FT, nonsignificant statistical difference) (Nielsen et al., 2010). Sixteen-year mortality in the same study population was 50.5% in the pPCI-treated patients (51.3% with FT, difference not statistically significant) (Thrane et al., 2020).

Danchin et al. studied 1492 consecutive STEMI patients in an observational study (Danchin et al., 2014) with a follow-up of five years: 447 patients were treated with FT, 583 had pPCI, and 462 had no reperfusion. Five-year mortality was 12% in FT, 17% in pPCI, and 41% with no reperfusion. There was no statistically significant difference in adjusted mortality when FT was compared with pPCI (HR 0.73, 95% CI 0.50–1.06, *P*=0.10).

According to the aforementioned studies, 30-day mortality of STEMI is around 2-11%, one-year mortality 4-15%, and after 10 years, at least one-third of the patients have died.

2.1.4 Treatment of Non-ST-elevation Acute Coronary Syndrome

The current European Society of Cardiology (ESC) guidelines recommend immediate (<2 hours) invasive evaluation with angiography for very high-risk patients with NSTE-ACS, including those with hemodynamic instability, life-threatening arrhythmias, and ongoing ischemic pain. Invasive evaluation within 24 hours is recommended for all patients with an established NSTEMI diagnosis and for patients with UA and high-risk features. Selective invasive strategy is chosen for patients with UA and who are low risk. (Collet et al., 2020)

Treatment of the disease-causing culprit lesion(s) with PCI, in most instances including a drug-eluting stent, is recommended. In the case of complex three-vessel disease or complex LM stenosis, urgent CABG may be necessary. Besides antithrombotic treatment, high-intensity statin started early is recommended for all NSTE-ACS patients. Beta-blocker therapy and treatment with ACEi or ARB is recommended for patients with reduced ejection fraction. Likewise, mineralocorticoid receptor antagonists are used in patients with low ejection fraction. (Collet et al., 2020; Freitas et al., 2019)

2.1.5 Prognosis of NSTEMI and Unstable Angina

STEMI has traditionally been considered the most severe form of MI, but the long-term outcome of NSTEMI may be as severe as that of STEMI.

According to one study, six-month mortality of NSTEMI patients decreased from 17.2% to 6.3% between 1995 and 2015, evidently as a result of better, more active treatment strategies (Puymirat et al., 2017). In a registry study by Montalescot et al, one-year mortality of NSTEMI was 11.6% (9% in STEMI) (G. Montalescot et al., 2007). Similarly, poor outcome of NSTEMI was reported during longer follow-up. In an observational cohort study with very long follow-up (median 12.7 years), the mortality of NSTEMI, STEMI, and UA were 61%, 58%, and 42%, respectively ($p<0.0001$) (Ellis et al., 2019).

Risk scores have been developed to assess the outcome in NSTE-ACS. The Thrombolysis in Myocardial Infarction (TIMI) risk score can be used to assess the risk of all-cause death, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization (Antman et al., 2000). The seven parameters utilized in the TIMI risk score are: 1) age ≥65 y, 2) ≥3 risk factors for coronary artery disease, 3) prior coronary artery stenosis of ≥50%, 4) ST-segment deviation in the ECG at

presentation, 5) ≥2 anginal events in prior 24 hours, 6) use of aspirin in prior 7 days, and 7) elevated cardiac markers of myocardial necrosis. The event rate during 14-day follow-up was 40.9% for a TIMI score of 6-7 and only 4.7% for a TIMI score of 0-1. (Antman et al., 2000)

The Global Registry of Acute Coronary Events (GRACE) risk score is used to assess ACS mortality. The score consists of several clinical parameters assessed at hospital discharge: age, no PCI during the hospital stay, history of congestive heart failure or MI, elevated resting heart rate, low systolic blood pressure on admission, ST depression, elevated initial creatinine level, and elevated markers of myocardial necrosis. The GRACE risk score was shown to predict mortality in all ACS groups, both in the short (six months) and long term (up to four years). (Tang, Wong, & Herbison, 2007)

Adding left ventricle ejection fraction to the GRACE score improves the prediction of six-month mortality in ACS (Syyli et al., 2019).

The Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using InTegrilin (PURSUIT) risk score predicted mortality or re-infarction at 30 days in NSTE-ACS. Variables used in this model are: 1) age; 2) gender; 3) worst Canadian Cardiovascular Society (CCS) class in the last six weeks; 4) heart rate; 5) systolic blood pressure; 6) signs of heart failure (rales); and 7) ST depression on the presenting ECG. (Boersma et al., 2000)

In a head-to-head comparison, the GRACE risk score showed better accuracy in predicting one-year mortality or MI than the TIMI or PURSUIT risk scores (de Araujo Goncalves, Ferreira, Aguiar, & Seabra-Gomes, 2005).

All the risk scores mentioned above include several clinical parameters and are somewhat complex. ECG can be used to assess the prognosis in NSTE-ACS as well. The next sections will review the prognostic value of different ECG morphologies and parameters in STEMI and NSTE-ACS.

2.2 ECG in Acute Coronary Syndromes

The electrocardiogram (ECG) in its most basic form was invented in the late 19th and the early 20th century (AlGhatrif & Lindsay, 2012). Since then, ECG has become a cornerstone of diagnostics in cardiology. Nowadays, the most fundamental classification of ACS into STEMI and NSTE-ACS is based on ST-segment analysis

in the ECG. A standard ECG comprises 12 leads – three bipolar limb leads (I, II and III), three unipolar augmented limb leads (aVL, aVF and aVR) and six unipolar precordial leads (V1-V6). When myocardial ischemia is suspected, 2-5 additional leads are recommended. Lead V4R is the preferred right-sided additional lead to enable detection of RV ischemia. At least one of additional leads V7-V9, which are placed on the posterior thorax, are recommended to improve detection of myocardial ischemia of the lateral (previously named posterior) LV wall. (Collet et al., 2020; B. Surawicz & T. Knilans, 2008b)

2.2.1 Origin of the QRS Complex and T Wave

The ECG measures differences in the membrane potential in the myocardium. Both depolarization and repolarization alter the membrane potential. When the whole myocardium is either depolarized or repolarized, there is no voltage recorded between the different myocardial areas, and the ECG recording is isoelectric. (B. Surawicz & T. Knilans, 2008b) The waves in the ECG, originally named by the Dutch physiologist Willem Einthoven, reflect depolarization and repolarization of the chambers of the heart (Hurst, 1998).

Cardiac electrical activation, which induces myocardial depolarization, starts in the sinoatrial node. The P wave reflects depolarization of the atria. During the PR interval, the whole atrial myocardium is depolarized. Repolarization of the atria results in a small-amplitude wave that is usually hidden under the QRS complex. (B. Surawicz & T. Knilans, 2008b) The depolarization wave enters the ventricles via the atrioventricular node and the bundle of His. The direction of depolarization is from the endocardium toward the epicardium and from the septum toward the other ventricular regions, with the basal posterolateral area of the LV being the last to depolarize. The electrical activation of the LV normally takes no longer than 80-90 ms, which is roughly the duration of a normal QRS complex. (Strauss, Selvester, & Wagner, 2011)

Repolarization of the ventricles takes place in a reversed order i.e., from the epicardium toward the endocardium. Normally, this results in a T-wave axis which is close to the QRS axis, and therefore in most leads, a positive QRS complex is followed by a positive T wave. (de Luna et al., 2014)

2.2.2 The Electrophysiological Background of Ischemic ST Elevation

The QRS complex depicts depolarization of the ventricles, whereas repolarization of the ventricles results in the T wave. Thereby, the ST segment depicts the part of systole where the ventricles are depolarized, and repolarization has not yet begun. In a normal heart, there are only minor voltage differences across the ventricles and the ST segment is virtually isoelectric. (B. Surawicz & T. Knilans, 2008a)

The ischemic myocardium remains less depolarized (less positively charged) than the rest of the heart. This creates a current toward the ischemic area during systole. In the ECG, this is reflected as elevation of the ST segment. The ST elevation is further enhanced by the potential difference in diastole. The ischemic area is less repolarized (less negatively charged) than the surrounding myocardium. This creates current away from the ischemic area causing depression of the TP segment. However, only enhanced ST elevation – not TP-segment depression – is recognizable, because the TP segment represents the baseline in the ECG recording. (Kleber, 2000; B. Surawicz & T. Knilans, 2008a).

ST elevation was traditionally thought to reflect infarct transmurality. However, recent studies with cardiac magnetic resonance (CMR) imaging have shown that ST elevation more accurately predicts infarct size than transmural extension of the infarct (Sarafoff et al., 2013).

2.2.3 Role of the ECG in Patients with Suspected ACS

Acquisition of an ECG within 10 minutes of the first medical contact is recommended when myocardial ischemia is suspected. Rapid evaluation of the ECG findings on-site or via telemedicine by medical personnel, mostly by a physician, is equally important. Working diagnoses of STEMI and NSTE-ACS are made according to the clinical context and the ECG findings. The first ECG diagnosis is crucial, as the treatment strategies of these two clinical entities are different. Repeated ECG recordings should be acquired, especially when the first ECG is non-diagnostic, or when there are definite changes in the symptoms. (Collet et al., 2020)

2.3 STEMI and ECG

2.3.1 Definition of STEMI

From an ECG standpoint, STEMI is defined as new-onset, persistent ST elevation. Pathological ST elevation in two contiguous leads (except for the additional leads) is required for the diagnosis. In leads aVL, I, II, aVF, III, V1, V4-V6 and V4R, pathological STE is defined as 1 mm measured at the J point (with standard calibration 10mm/mV). In posterior leads V7-V9, an STE of >0.5 mm is considered abnormal (Wong, 2011). In leads V2-V3, pathological STE, measured at the J point, is defined as ≥1.5 mm in women, ≥2 mm in men ≥40 years of age, and ≥2.5mm in men less than 40 years of age. This definition applies only in the absence of confounding factors such as LBBB or LVH. (Ibanez et al., 2018; Thygesen et al., 2018)

2.3.2 STEMI Equivalents

The routine 12-lead ECG covers some areas of the heart better than others. Ischemia in the basal inferior LV or parts of the lateral LV wall may not be detected by the standard 12-lead ECG. However, reciprocal ST depressions in leads V1-V3 may reveal inferolateral (formerly named posterior) ischemia (Meyers et al., 2021). Acquiring a 15-lead ECG with posterior leads may confirm the diagnosis. (Thygesen et al., 2018; Wong, 2011)

In a large study, right bundle branch block (RBBB) – often without ST elevation – was associated with poor prognosis and STEMI-like angiographic findings (Widimsky et al., 2012). The ESC guidelines recommend urgent invasive evaluation for patients with RBBB and symptoms indicating acute MI (AMI) (Ibanez et al., 2018). This interpretation has been criticized, as discussed later.

Upsloping ST depression followed by tall positive T waves in the precordial leads may imply occlusion of the LAD. This is often accompanied by ST elevation in lead aVR. A patient with symptoms of ACS and this "de Winter sign" in the ECG should be treated similar to STEMI. (de Winter, Verouden, Wellens, Wilde, & Interventional Cardiology Group of the Academic Medical, 2008)

In acute transmural ischemia, the ECG manifestations may evolve over time. Restoration of blood flow or development of myocardial necrosis result in ST resolution (STR), often with Q waves and TWIs. These ECG findings, when present in the acute phase ECG, should be considered "STEMI equivalents," even in the absence of persistent ST elevation. (K. Nikus et al., 2010) In the setting of UA, the so-called Wellens' sign – deep and symmetrical TWIs in the precordial leads – is associated with critical stenosis of the LAD. This ECG sign may in some cases represent evolution of anterior STEMI. (de Zwaan et al., 1989)

Single-lead STE in lead III combined with ST depression and positive T wave in any of leads V4-V6 and with ST elevation in V1>V2 often implies inferior MI. There is often a significant stenosis or occlusion in the infarct-related artery and multivessel disease. LCx is the most common culprit artery associated with this pattern. (E. Aslanger et al., 2020)

Reciprocal ST depression in lead aVL can predict inferior MI even when the ST elevations in the inferior leads do not exceed the threshold for STEMI diagnosis (Y. Birnbaum, Sclarovsky, Mager, Strasberg, & Rechavia, 1993). These patients should be treated as STEMI in the setting of acute chest pain.

2.3.3 Occlusive vs. Non-occlusive Myocardial Infarction

As already discussed, there are ECG signs of an occluded coronary artery that do not fulfill the established STEMI criteria. In other words, acute coronary artery occlusion is not equivalent to STEMI, and nearly one-third of patients with acute coronary occlusion (ACO) do not fulfill the ECG criteria for STEMI (Abbas et al., 2004; Schmitt et al., 2001). NSTEMI patients with a total coronary occlusion have higher risk of death and adverse events compared with those without an acute total occlusion (Khan et al., 2017). In the DIFOCCULT study, several different ECG parameters were used along with ST elevation to predict ACO. These parameters were minor ST elevation with reciprocal ST depression; subtle anterior ST elevation with terminal QRS distortion; subtle anterior ST elevation with certain formulas confirming ischemic ST elevation; subtle inferior ST elevation with ST depression in lead aVL; non-contiguous ST elevation (I, aVL, V2 for diagonal branch occlusion; III, V1, and ST depression in leads V4-6 for inferior MI); anterior ST depression implying inferolateral MI; the de Winter sign (upsloping anterior ST depression with tall T waves); and hyperacute (tall and pointed) T waves. Using these criteria, a sensitivity of 73.6% and specificity of 90.1% was reached for ACO. The STEMI

criteria yielded sensitivity and specificity of 70.5% and 88.0%, respectively. The p value for the difference between the two criteria was 0.026. (E. K. Aslanger et al., 2020)

Meyers and colleagues used a slightly different definition for "occlusive MI" (OMI) than was used in the DIFOCCULT study. They applied eight criteria: subtle ST elevation not fulfilling the STEMI criteria; hyperacute T waves including the de Winter sign; ST depression interpreted as reciprocal and/or negative hyperacute T waves; ST depression in V1-V4 suggestive of inferolateral MI; Q waves with subtle ST elevation suggesting acute ischemia; terminal QRS distortion with subtle ST elevation; any inferior ST elevation with ST depression or TWI in aVL; and LBBB or ventricular paced rhythm indicating coronary artery occlusion according to the modified Sgarbossa criteria. The STEMI criteria had 36-41% sensitivity for ACO, while sensitivity of the OMI criteria was 80-86%. Specificity was 91-94% and 91-92% in the respective groups. (Pendell Meyers et al., 2021)

2.3.4 ECG-based Risk Stratification in STEMI

There are several risk scores for ACS, but only a few that were specifically constructed for risk stratification in STEMI. Most of the risk scores include several clinical parameters, such as blood pressure and age, in assessing the risk of death (Lev et al., 2008). These risk scores have little use in clinical practice, as the treatment choices in STEMI patients do not depend on the risk scores. The following reviews ECG-based risk scores and the prognosis of certain ECG morphologies in STEMI.

2.3.4.1 Risk Scores

The cumulative sum of ST elevation can be used to predict patient outcomes in STEMI (Vermeer et al., 1986). The accuracy of risk stratification can be improved by using the combined sum of ST elevations and ST depressions (Postma et al., 2016). However, the absolute amount of ST deviation may vary independently of the extension and severity of ischemia. For example, chronic obstructive pulmonary disease (COPD) may attenuate all waves in the ECG and thus lower the sum of ST deviations. Ischemia of anatomically opposite walls may also attenuate the ST changes when the ischemic area is large. Theoretically, combining assessment of ST and QRS changes – as in the grades of ischemia (discussed later) – could be more accurate.

The Selvester score, introduced by Ronald H. Startt-Selvester and Galen S. Wagner, is a combined assessment of different features of the QRS complex and can be used to assess infarct size after STEMI, although it is not as accurate as troponin (Tiller, Reindl, Reinstadler, et al., 2019). The original version of the Selvester score comprises 54 variables, whereas the simplified version has 37 criteria (Bounous et al., 1988; Selvester, Wagner, & Hindman, 1985).

The Anderson-Wilkins (AW) acuteness score was developed as a tool to discover myocardial salvageability in STEMI. In the AW score, Q waves and tall T waves are used to assess the electrocardiographic acuteness of STEMI. The AW score is more accurate than historical timing, at least in some types of STEMI. The AW score is not used to assess mortality. (Corey et al., 1999)

These ECG scores have not been widely implemented as practical tools in everyday clinical practice. Combining the ECG scores in automated ECG analysis software could be useful.

2.3.4.2 Infarct Localization

In comparison with the inferior location, MI in the anterior location was associated with higher in-hospital and long-term mortality as well as higher incidence of heart failure in a study from the late 1980s (Stone et al., 1988). In that study, MIs were classified according to the presence of new Q waves. In the era of reperfusion therapies, STEMI in the anterior location was shown to predict higher 30-day mortality compared with the non-anterior MI location (K. L. Lee et al., 1995). In anterior STEMI, the typical culprit artery is the LAD. A large registry study showed higher short- and long-term mortality in STEMI patients with the LAD as the culprit artery compared with LCx or RCA culprit arteries (Entezarjou, Mohammad, Andell, & Koul, 2018). In a study with pPCI patients, anterior STEMI was associated with worse outcome than non-anterior STEMI, but this was explained by more extensive myocardial injury confirmed by CMR (Reindl et al., 2020). Consequently, it may be that the MI localization does not matter but the size does. Anterior MIs may be more dangerous due to the larger area-at-risk.

2.3.4.3 Grades of Ischemia

The grades of ischemia were introduced and later refined by Samuel Sclarovsky and Yochai Birnbaum in the 1990s as a tool for risk stratification in STEMI (Y. Birnbaum, Herz, et al., 1996; Y. Birnbaum, Sclarovsky, Blum, Mager, & Gabbay, 1993; Sclarovsky et al., 1990). In this classification, acute ischemia is divided into three categories. Grade 1 ischemia is defined as tall T waves with no ST elevation. STEMIs are classified as grade 2 ischemia (G2I) when there is no distortion of the terminal portion of the QRS complex, and grade 3 ischemia (G3I), where the terminal portion of the QRS complex is affected by the ischemic process. (Billgren et al., 2004) Only G2I and G3I are reviewed here, as grade 1 ischemia is, by definition, not a STEMI.

Distortion of the terminal portion of the QRS complex is defined differently in different ECG leads. In the leads with an rS type complex – typically V1-V3 – G3I is defined as disappearance of the S wave. In the leads with a qR type complex – typically all other leads – G3I is defined as J point elevation≥ 50% of the height of the R wave (Figures 1 and 2). Grades of ischemia are only applicable in supraventricular beats and in the absence of LVH, pre-excitation, low voltage ECG or BBB. (Billgren et al., 2004)

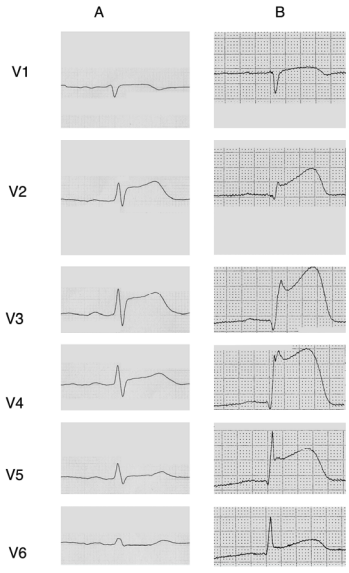

Figure 1. Anterior G2I (A) and G3I (B).

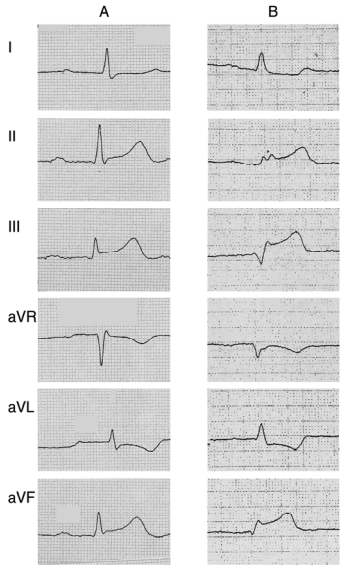

Figure 2. Inferior G2I (A) and G3I (B).

2.3.4.3.1 Pathophysiology of Grade 3 Ischemia

The pathophysiology behind G3I is not precisely known. It is thought that severe ischemia of the Purkinje fibers of the cardiac conduction system leads to slower conduction in the ventricle manifested as G3I in the ECG (Y. Birnbaum & Sclarovsky, 2001). The Purkinje fibers are relatively resistant to hypoxia and not affected by mild ischemia (Lazzara, el-Sherif, & Scherlag, 1974). This theory is fortified by clinical data that showed less probability of collateral flow (Garcia-Rubira, Nunez-Gil, et al., 2008), less pre-MI angina (i.e. less ischemic preconditioning) (Y. Birnbaum, Kloner, et al., 1996), less residual flow through the culprit artery (Sejersten et al., 2006), higher thrombus burden (Kurt, Karakas, Buyukkaya, Akcay, & Sen, 2014), and more microvascular damage (Weaver et al., 2011) in STEMI patients with G3I compared with G2I.

2.3.4.3.2 Impact on Outcome

Myocardial ischemia in G3I progresses to necrosis faster than in G2I. Ringborn et al. studied STEMI patients with single-photon emission computed tomography (SPECT) and found that pre-hospital G3I and G2I had similar myocardial salvage with pPCI when treated early. In STEMI patients treated >2.5 hours after symptom onset, myocardial salvage was lower in G3I than in G2I (48% vs. 62%, p=0.04) (Ringborn et al., 2014). G3I resulted in larger infarcts (Y. Birnbaum, Kloner, et al., 1996) and a lower post-infarct left ventricular ejection fraction (Y. Birnbaum, Criger, et al., 2001).

One of the first studies dealing with the issue of grades of ischemia, including patient outcome, by Birnbaum et al. in 1996, showed an in-hospital mortality rate of 6.8% in G3I and 3.8% in G2I (p=0.0008) in STEMI patients, who underwent FT (Y. Birnbaum, Herz, et al., 1996). In a study comparing FT with pPCI, G3I was associated with higher in-hospital mortality compared to G2I (6.8% vs. 3.2%, p=0.016). The selected treatment did not affect outcomes within ischemia grades (Y. Birnbaum, Goodman, et al., 2001). McGehee et al. studied consecutive STEMI patients treated with pPCI. They reported a 1% (n=1) in-hospital mortality rate in G3I and 3% (n=3) in G2I, but the difference lacked statistical significance (p=0.84). (McGehee et al., 2007). Garcia-Rubira et al. also studied the in-hospital outcome of pPCI-treated STEMI patients. In-hospital mortality was 6% (n=6) in patients with terminal QRS distortion and 3% (n=11) in those without, p=0.094 (Garcia-Rubira,

Garcia-Borbolla, et al., 2008). Of note, their definition of terminal QRS distortion differed slightly from other studies.

In the DANAMI-2 trial, patients with G3I had 9.7% 30-day mortality, compared with 4.8% in G2I, p<0.001 (Sejersten et al., 2006). In the ON-TIME 2 study of pPCI patients, 30-day mortality was 5.1% in G3I and 2.1% in G2I, p=0.004, and G3I was an independent predictor of 30-day mortality in the multivariable analysis (OR 3.2, 95% CI 1.2-8.7) (Postma et al., 2011). Lee et al. assessed the prognostic significance of ECG findings in 153 consecutive pPCI patients; G3I was found in 41 patients. None of the study patients (neither G3I nor G2I) died during the six-week follow-up (C. W. Lee et al., 2001).

In the TIMI-4 study, the one-year mortality of STEMI patients undergoing FT was 18% in G3I and 6% in G2I, p=0.03 (Y. Birnbaum, Kloner, et al., 1996). One-year mortality was 7.0% in G3I and 3.7% in G2I (p=0.010) in the ON-TIME 2 study. (Postma et al., 2011). Higher one-year mortality in G3I was also reported in the TOTAL trial (5.2% vs. 3.3% in G2I, p<0.001). In the multivariable analysis there was no independent association between G3I and one-year mortality (adjusted HR 1.25, 95% CI 0.94-1.65). (Leivo et al., 2021) Rommel et al. studied the CMR findings of pPCI-treated STEMI patients with G3I and G2I. One-year mortality was 3.3% and 2.1% in the respective groups. The difference between the groups lacked statistical significance (p=0.39) (Rommel et al., 2016).

Real-life data on outcomes of patients based on the grades of ischemia is scarce. Yilmaz et al. studied consecutive STEMI patients in a real-life setting (Yilmaz et al., 2019). Their study included both pPCI- and FT-treated patients and the study was observational. Notably, the investigators used non-ECG exclusion criteria, including previous MI or CABG and symptom onset >24 hours before admission. Also, patients not eligible for ischemia grading were excluded. In-hospital mortality was 17.2% in G3I and 4.8% in G2I, respectively, p<0.001. The investigators reported a 36-month follow-up, and mortality at the end of the study was 35.4% in G3I and 19.5% in G2I, p=0.01.

A recent registry study investigated long-term outcome of pPCI patients. G3I was not associated with higher mortality during 3.7-year follow-up when compared to G2I (HR 0.79, 95% CI 0.53-1.16). When adjusted with age and diseases, there was no statistically significant association between G3I and higher mortality either. (Lahti et al., 2022)

In general, there is no evidence to show the superiority of pPCI over FT in G3I (Y. Birnbaum, Goodman, et al., 2001). In the DANAMI-2 trial, there was a tendency toward better outcomes in early-presenting G3I patients treated with pPCI. The rate of re-infarction was higher in late-presenting G3I patients treated with FT. (Sejersten et al., 2006)

2.3.4.3.3 Limitations of the Grades of Ischemia

Most of the studies on the grades of ischemia are post-hoc analyses of randomized controlled trials. These trials had numerous exclusion criteria. Some representative studies on the grades of ischemia in STEMI are shown in Table 1. (Y. Birnbaum, Goodman, et al., 2001; Y. Birnbaum, Kloner, et al., 1996; Y. Birnbaum, Sclarovsky, Blum, et al., 1993; Leivo et al., 2021; McGehee et al., 2007; Postma et al., 2011; Sejersten et al., 2006) The proportion of G3I in STEMI patients eligible for ischemia grading varied roughly between 20 % and 45% in the published studies. Table 1 also shows the number of excluded patients in each study. Per definition, ischemia grading excludes a remarkable proportion of STEMI patients with high-risk features, such as those with broad QRS or TWIs (Billgren et al., 2004).

Table 1. Non-ECG-related exclusion criteria and the proportion of G3I patients in a number of studies on the grades of ischemia.

Study	Non-ECG-related exclusion criteria	Proportion of GI 3 (of GI 2 + GI 3)
Birnbaum 1993	-prior AMI -non-anterior AMI	58/135; 43.0%
Birnbaum 1996 **TIMI-4**	-age >80 years -contraindication to FT -recent CABG -previous use of streptokinase or anistreplase -women of childbearing potential -use of oral anticoagulation therapy -presence of any other serious disease	85/378; 22.5%
Birnbaum 2001 **Gusto IIb**	-use of warfarin -active bleeding -history of stroke -contraindication to heparin therapy -renal insufficiency (serum creatinine >177μmol per liter) -systolic blood pressure more than 200 mmHg or diastolic blood pressure of more than 110 mmHg -women of childbearing potential	278/894; 31.1% (27.5% of all)
Sejersten 2006 **DANAMI-2**	-contraindication to FT -acute MI and FT within the previous 30 days -pulseless femoral arteries -previous CABG, chronic renal failure -diabetes treated with metformin -non-ischemic heart disease -non-cardiac disease associated with a life expectancy of less than 12 months -cardiogenic shock -severe heart failure (systolic blood pressure <65 mmHg) -persistent life-threatening arrhythmias -need for mechanical ventilation	360/1319; 27.3%
McGehee 2007	-none (only pPCI-treated patients included)	66/155; 42.6%
Postma 2011 **On-TIME**	-therapy-resistant cardiogenic shock -renal dysfunction -persistent severe hypertension -contraindication to anticoagulation -increased bleeding risk -pregnancy or breastfeeding -life expectancy of less than 1 year	426/1308; 32.6%
Leivo 2021 **TOTAL**	-age ≤ 18 years -prior CABG -life expectancy less than six months due to non-cardiac condition -treatment with FT for qualifying index STEMI event	1563/7211; 21.6%

2.3.4.3.4 ECG Categories Resembling G3I

So-called tombstoning STEMI with ST elevation above the R wave is associated with poor prognosis (Balci, 2009). This entity may in most cases represent G3I, although it is defined differently.

A triangular QRS-ST-T waveform is also a subtype of G3I. In this pattern, the QRS complex and T wave have merged to form a single triangular wave. This phenomenon is rare, but is associated with high incidence of primary ventricular fibrillation and high mortality. (Cipriani et al., 2018; Cipriani et al., 2021)

2.3.4.4 Pathological Q Wave in STEMI

In The Fourth Universal Definition of Myocardial Infarction (Thygesen et al., 2018), pathological Q waves are defined as follows:

Any Q wave > 0.02 s or QS complex in leads V2-V3.

Q wave ≥ 0.03 s and ≥ 1 mm deep or QS complex in leads I, II, aVL, aVF, V4-6 in any two leads of a contiguous lead grouping (I, aVL; V4-V6; II, III, aVF). The same criteria are used for supplementary leads V7-V9.

R wave > 0.04 s in V1-V2 and R/S > 1 with a concordant positive T wave in absence of conduction defect.

According to the Universal Definition, several non-MI confounders may lead to Q waves:

- LBBB
- Pre-excitation
- Left anterior hemiblock
- LVH
- Right ventricular hypertrophy
- Cardiomyopathy
- Takotsubo syndrome

- Cardiac amyloidosis
- Hyperkalemia
- Myocarditis
- Acute cor pulmonale

Practically any cardiac condition that affects the QRS complex may influence the accuracy of detecting MI-related Q waves.

Pardee was the first to describe the development of permanent Q waves after MI in a patient with ST elevation in the acute phase as early as 1920 (Pardee, 1920). From then, Q waves in the ECG were traditionally thought to reflect infarcted myocardium. This concept was later fortified by studies comparing ECG findings with postmortem autopsy findings (Horan, Flowers, & Johnson, 1971).

In a study published in 1954 with 19 experimental dogs by Prinzmetal et al, subendocardial infarcts did not affect the QRS complex (Prinzmetal et al., 1954). This famous study led to a widespread misconception that Q waves only reflect transmural infarcts. Later, it was well-documented that Q waves are often seen in subendocardial infarcts as well (Raunio et al., 1979). Traditionally, MIs were classified as Q-wave MIs and non-Q-wave MIs (Herlitz, Karlson, Sjolin, & Lindqvist, 2001; Keen et al., 1994).

The role of Q waves is more diverse in the acute phase of myocardial ischemia. In early canine models, Q waves were seen in the reperfusion phase when an occluded coronary artery was opened (Blumenthal, Wang, & Pang, 1975; Bodenheimer, Banka, Levites, & Helfant, 1976). In human studies, Q waves have been found in the early stages of the infarct process (Raitt et al., 1995), but this is not considered to be due to reperfusion. Quite to the contrary, angiography more often shows thrombus or total occlusion of the infarct-related artery in patients with Q waves, whereas collateral flow from non-occluded arteries to the occluded artery is less often observed (Keen et al., 1994). In acute STEMI, Q waves may reflect irreversible damage and necrosis. A study comparing findings in positron emission tomography/computed tomography (PET-CT), echocardiography, and ECG in AMI patients found that ischemic and viable myocardium was more common in the absence of Q waves (91% vs. 61%, $p<0.05$) (Yang et al., 2004). However, modern imaging modalities and serial ECG recordings through the acute phase of ischemia

have revealed that Q waves may be transient, and they may sometimes reflect a large area-at-risk rather than permanent necrosis (Delewi et al., 2013).

Many studies have confirmed that Q waves reflect larger infarcts. An MRI study by Moon et al. showed low correlation between Q waves and infarct transmurality, which was in line with earlier autopsy studies. In this study, Q waves predicted larger infarct size. (Moon et al., 2004) In another MRI study, more microvascular damage was seen in patients with Q waves (Tiller, Reindl, Holzknecht, et al., 2019). Higher peak creatine kinase levels (Y. Birnbaum et al., 1997) and cTn levels (Armstrong et al., 2009) are seen in patients with Q waves, also implying larger infarcts.

Larger infarcts with worse angiographic findings logically result in worse outcomes in patients with Q waves compared to those without Q waves. In STEMI patients treated with PCI, higher one-year mortality was seen in patients with than without Q waves (4.9% vs. 2.8%, $p<0.001$) (Siha et al., 2012). This had also been confirmed earlier in studies of patients treated with FT. Wong et al. reported higher 30-day mortality in patients with initial Q waves than in those without (10% vs. 7%, $p<0.0001$) (Wong, Gao, Raffel, et al., 2006). Higher mortality in patients with Q waves in their ECG is independent of time from symptom onset (Armstrong et al., 2009; Siha et al., 2012). Q waves diminish the benefit gained from reperfusion therapy. In STEMI patients with Q waves, there is less post-treatment antegrade flow and less ST resolution (Armstrong et al., 2009; Wong et al., 1999; Wong et al., 2002). Q waves still do not cancel the benefit of reperfusion therapy in otherwise eligible patients – instead, the risk for adverse outcome associated with Q waves can be lowered with reperfusion therapy. (Raitt et al., 1995)

2.3.4.5 T-wave Inversion in STEMI

In his detailed, groundbreaking report of ECG changes in a 38-year male suffering an AMI in 1920, Harold E.B. Pardee noticed that during the evolving stages of the AMI, T waves first become tall and then gradually inverted (Pardee, 1920). T waves reflect repolarization of the ventricles. In myocardial necrosis, T waves become inverted as the repolarization current is turned away from the diseased area. TWI is seen in myocardial reperfusion after ischemia as well, although this phenomenon is practically the opposite of myocardial necrosis. (Fiol-Sala, 2019)

In STEMI, development of permanent TWI was traditionally linked to later stages of the infarct process and established myocardial necrosis (Bosimini et al.,

2000; Pardee, 1920; Reindl et al., 2017). However, not all TWIs are permanent in STEMI, and TWI does not always reflect a late phase of myocardial ischemia and necrosis. Several studies have reported TWI in STEMI patients presenting early after symptom onset (Alsaab et al., 2014; Herz et al., 1999). In a study by Herz et al., late presenters with TWI had adverse outcomes, whereas early presenters did not. None of the 52 TWI patients presenting <2 hours from symptom onset died during the hospital stay, compared to 5% of the 726 patients with no TWI, p=0.19. The percentages in the respective categories were 10.2% and 5.4% (p=0.01), respectively, in patients presenting >2 hours from symptom onset. (Herz et al., 1999)

In many studies, TWI has been a sign of successful reperfusion therapy predicting patency of the infarct-related artery (IRA) and favorable outcome (Corbalan et al., 1999; Doevendans et al., 1995; M. J. Lee et al., 2017). However, in the presenting ECGs, both IRA patency (Alsaab et al., 2014; Hira, Moore, Huang, Wilson, & Birnbaum, 2014) and non-patency (Shimada, Po, Kanei, & Schweitzer, 2013) have been reported. Whether TWI predicts patency or non-patency of the IRA may depend on the time from symptom onset to the ECG recording, as discussed later.

As the patency and non-patency rates vary among studies, the outcome of TWI also varies. TWI has been reported to predict better LV function and R-wave recovery (Agetsuma et al., 1996). In a study with a long mean time from symptom onset to hospital (28 hours and 15 hours in TWI and no TWI, respectively), patients with TWI had higher risk of major adverse cardiovascular events (MACE) (35% vs. 17%, p=0.007), a longer hospital stay, and more often inadequate STR (78% vs. 44%, p<0.001) (Shimada et al., 2013).

2.3.4.6 Pre-infarction Syndrome and Evolving Myocardial Infarction

As mentioned above, Q waves and TWIs were considered as ECG signs of an established MI already in the early 20th century. Later studies confirmed the prognostic value of these two ECG changes. In his textbook, Samuel Sclarovsky combined these two ECG markers of evolving myocardial infarction in STEMI and found the combination useful to establish the temporal phases of the disease process. Accordingly, STEMI with Q waves and/or TWIs was defined as evolving myocardial infarction (EMI), while the absence of these changes was named pre-infarction syndrome (PIS). (Sclarovsky, 1999)

The clinical significance of the PIS and EMI categories has been less studied than that of Q waves and TWIs as separate entities. In the DANAMI-2 trial, STEMI patients with PIS benefited from PCI over FT ($p=0.01$ for the difference of survival between the treatment groups), whereas patients with EMI did not ($p=0.19$). However, anterior EMI with positive T waves benefited from pPCI over FT (composite endpoint in 39% in FT vs. 20% in pPCI, $p=0.008$). (Eskola et al., 2007). A substudy of the TOTAL trial showed worse outcomes in patients with EMI than with PIS (10.4% vs. 6.1%, $p<0.001$). The endpoint in that study was a composite of death from cardiovascular (CV) causes, recurrent MI, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within one year. All-cause mortality at one year was 5.7% in EMI and 3.2% in PIS, $p<0.001$. (Leivo et al., 2020).

There is low inter-rater variability in the interpretation of PIS and EMI categories among clinicians (Koivumaki et al., 2015).

2.3.4.7 Broad QRS in STEMI

The QRS complex reflects depolarization of the ventricles of the heart. Normal electrical conduction via the cardiac conduction system may be disturbed in myocardial ischemia, which results in widening of the QRS complex (Cantor, Goldfarb, & Ilia, 2000). Damage in the left bundle branch causes LBBB, while diseases affecting the right bundle branch results in RBBB in the ECG. STEMI may be the cause of BBB if the region of myocardial ischemia or infarction involves the bundle branch (K. Nikus, Birnbaum, Fiol-Sala, Rankinen, & de Luna, 2021).

Broadening of the QRS complex alters the ST segment and the T wave, resulting in secondary ST-T changes, which make it challenging to discern STEMI. Substantial ST elevations in leads with a negative QRS complex may be seen in LBBB and other ECGs with wide QRS without any ischemia (Deshpande & Birnbaum, 2014). In previous guidelines, new or presumably new LBBB was considered a STEMI equivalent (Antman et al., 2004). However, more recent studies showed that LBBB (neither old nor presumably new) did not increase the likelihood of MI in patients treated with suspected ACS (Chang et al., 2009). The significance of LBBB in ACS and AMI is covered in the NSTEMI section, as LBBB is no longer considered a STEMI equivalent.

The right bundle branch of the intraventricular conduction system is perfused via the LAD (James & Burch, 1958). Thus, occlusion of the proximal LAD often results

in RBBB, and RBBB is known to predict higher mortality in STEMI. In pPCI patients, RBBB was more often associated with LAD occlusion (61% vs. 42%, p<0.001), proximal occlusion (60% vs. 46%, p=0.004), and higher in-hospital mortality (17% vs. 5%, p<0.001) than absence of RBBB (Vivas et al., 2010). High mortality was reported in a large registry study in patients with anterior STEMI and RBBB – in-hospital mortality was 15.3% in patients with RBBB and 9.2% in patients without, p<0.0001. RBBB was independently associated with in-hospital mortality in the multivariable analysis (HR 1.66, 95% CI 1.52-1.81) (Shrivastav et al., 2021). Wider QRS in anterior STEMI and RBBB led to higher mortality in a study by Wong et al. (Wong, Gao, Stewart, et al., 2006). RBBB in inferior STEMI may not be an independent predictor of mortality. In FT-treated patients, new RBBB was independently associated with 30-day mortality in anterior STEMI (OR 3.84, 95% CI 2.38-6.22) but not in inferior STEMI (OR 2.23, 95% CI 0.54-9.21) (Wong, Stewart, et al., 2006). In a large study by Widimsky et al, pPCI patients with RBBB (with or without ST elevation) often (51.7%) had total occlusion of the infarct-related artery, and the in-hospital mortality rate was 14.3% for RBBB compared with 5.4% for STEMI without RBBB, p<0.001 for the difference between all ECG categories (Widimsky et al., 2012). In a large registry study of STEMI patients, RBBB predicted higher in-hospital mortality (12.8%) than LBBB (5%, p<0.001 for the difference between the two groups) or no BBB (3.1%, p<0.001) (Fernandes et al., 2020).

Based on the findings by Widimsky et al., the Fourth Universal Definition of Myocardial Infarction states that new or presumably new RBBB, even without associated ST-segment or T-wave changes, is associated with suboptimal TIMI 0–2 flow in as many as 66% of patients, while the corresponding rate was >90% in those with associated ST-segment or T wave changes (Thygesen et al., 2018). This interpretation has been criticized, as the patients studied by Widimsky et al. were not unselected patients with suspected ACS, but patients chosen for pPCI (Y. Birnbaum et al., 2020).

Nonspecific intraventricular conduction delay (IVCD) is defined as a wide QRS complex other than RBBB, LBBB, or pre-excitation (Aro et al., 2011). The prognostic significance of IVCD in STEMI has not been well-studied. In ACS patients with cardiogenic shock, IVCD was associated with higher mortality than no ventricular conduction block during one-year follow-up. The p value for one-year mortality in IVCD in the Cox regression analysis was 0.021, but the statistical significance was lost when adjusted with other variables (Tolppanen et al., 2018). In

a recent retrospective study of 1363 consecutive patients hospitalized for first STEMI, IVCD predicted all-cause mortality (HR 2.57, 95% CI 1.72-3.82) during the 3.7-year follow-up in all-comers with STEMI (Lahti et al., 2022).

2.3.5 ECG Signs of Reperfusion

In the era of FT, the post-procedure ECG yielded crucial information about the success of fibrinolysis. STEMI patients with failed reperfusion usually underwent rescue PCI. The significance of defining post-procedure reperfusion has declined, as pPCI has become the golden standard therapy in STEMI (Ibanez et al., 2018). Nowadays, post-procedure ECG mostly serves as a tool for risk stratification in STEMI patients treated with pPCI.

Perhaps the most widely used sign of reperfusion is ST resolution (STR). Spontaneous STR is an excellent predictor of culprit artery patency (Lemkes et al., 2019). STR after FT has been studied widely. STR predicts culprit artery patency after FT. In the TIMI 14 trial, STR >50% was associated with TIMI 2-3 flow in 90%, whereas the proportion was 67% in STR <50%, $p<0.0001$ (de Lemos et al., 2000). Lower 30-day cardiac mortality in STR was reported in FT-treated patients when treated within 4 hours from symptom onset (1.1% in complete STR, 3.1% in partial STR, and 9.2% in no STR, $p<0.001$) and also after 4 hours (1.9%, 5.4%, and 13.8% in the respective groups, $p<0.001$) (Zeymer et al., 2005). Several other studies have confirmed that post-fibrinolysis STR predicts good epicardial and microvascular flow as well as smaller infarcts, lower mortality, and lower incidence of congestive heart failure (de Lemos & Braunwald, 2001; R. Schroder, 2004). The ESC guidelines for STEMI recommend measuring STR at 60-90 minutes from the thrombolysis and using a cut-off of a 50% decrease of the amount of ST elevation compared with the pre-reperfusion ECG (Ibanez et al., 2018).

Many studies have investigated the prognostic significance of STR in STEMI patients treated with pPCI. STR <50% at the end of PCI predicted larger infarcts measured with the Selvester score in the ECG and cardiac enzyme release and was also associated with higher cardiac mortality (2% vs. 15%, $p=0.01$) (Claeys et al., 1999). STR <30% 60 minutes after pPCI predicted 8.4% three-year mortality as compared to 5.0% in STR 30-70%, and 5.6% in STR >70%, $p=0.03$ for all groups (Farkouh et al., 2013). The poor outcome of low STR is thought to reflect impaired microvascular flow even when epicardial flow has been restored (Claeys et al., 1999).

Successful reperfusion often leads to accelerated idioventricular rhythm (AIVR), which is a benign, relatively slow tachycardia originating in the reperfused ventricular myocardium. After FT, AIVR was associated with culprit artery patency. AIVR was seen in 25/63 patients with TIMI flow of 2-3 and in 1/19 patient with TIMI flow of 0-1, p=0.011 (Hohnloser, Zabel, Kasper, Meinertz, & Just, 1991). In a more recent study of pPCI patients, AIVR predicted worse epicardial flow on admission, larger area-at-risk, and larger final infarct size compared to patients without AIVR post-PCI (Terkelsen et al., 2009). The investigators concluded that AIVR is not necessarily a marker of successful reperfusion. However, reduction of ischemia (area-at-risk minus final infarct size) by PCI was higher in patients with AIVR.

As discussed previously, post-procedural TWI may also be a sign of successful reperfusion (M. J. Lee et al., 2017).

2.3.6 Non-ischemic Causes of ST Elevation

ST elevation in the ECG has many other etiologies than MI. Most types of the early repolarization phenomenon are considered as normal variants, and early repolarization is typically seen in the ECG of young men. Perimyocarditis may mimic STEMI, as the patient often presents with ST elevation and chest pain. However, while reciprocal ST depressions are very frequently seen in STEMI, they are rarely present in the ECG of patients with perimyocarditis, except for lead aVR. PQ-segment depression in both the inferior and the precordial leads aid in the differential diagnosis against STEMI, where PQ-segment changes are less frequent (Porela, Kyto, Nikus, Eskola, & Airaksinen, 2012). ECG in hyperkalemia typically shows tall T waves, but ST elevation may also occur. In Brugada syndrome, there is an R´ wave in the right-sided precordial leads accompanied by downsloping ST elevation and T-wave inversion. Pulmonary embolism may rarely cause ST elevation in the precordial leads due to right ventricular overload and subsequent dilation and ischemia. (Y. Birnbaum, Rankinen, Jneid, Atar, & Nikus, 2022; K. Wang, Asinger, & Marriott, 2003)

2.4 ECG in NSTE-ACS

2.4.1 ST Depression

The correlation between ST depression and subendocardial injury was found already in the 1940s (Bayley, 1946). Later experimental studies showed that ST depression may result from milder ischemia than ST elevation (Ekmekci, Toyoshima, Kwoczynski, Nagaya, & Prinzmetal, 1961).

In clinical practice and contrary to ST elevation, ST depression is not an equally uniform entity. ST depression may in fact often reflect similar pathophysiological processes to those associated with STEMI. ST depression in precordial leads V1-V4 may be the primary finding of inferolateral STEMI (Meyers et al., 2021) although isolated ST depression in these leads without any ST elevation in a 12-lead ECG was rare in another study (Meyers et al., 2021; Rokos et al., 2012). Using additional leads V7-V9 is recommended, especially when LCx occlusion is suspected (Thygesen et al., 2018).

In a large study on NSTEMI patients treated with PCI, 66% of the patients with an occluded culprit artery had the culprit lesion in the LCx (Dixon et al., 2008). Another study showed that patients presenting with NSTE-ACS and an occluded culprit artery more often had the culprit lesion in the inferolateral ventricular region. More than half of the NSTE-ACS patients had ST depression. There was no difference in the incidence of ST depression between patients with occluded and non-occluded arteries. (T. Y. Wang et al., 2009)

These studies imply that many infarcts, especially those caused by LCx occlusion, are reflected as ST depression or other NSTE morphologies, even if the artery is occluded.

Occlusion of the proximal LAD may rarely result in anterior ST depression. The "de Winter sign" was originally defined as upsloping ST depression in the anterior leads combined with tall, positive symmetrical T waves in the affected leads. The de Winter sign should be considered as a STEMI equivalent, as mentioned earlier. (de Winter et al., 2008; Verouden et al., 2009)

Extensive ST depressions and TWIs are the main findings in global ischemia (discussed later in detail) (K. C. Nikus et al., 2004). Anatomical correlations and outcomes of ST depression have mostly been covered in studies of patients with

global ischemia. This entity is reviewed later, and the studies mentioned in this section include all ACS patients with ST depression.

Using the Q/non-Q categorization of AMI, ST depression in non-Q-AMI may reflect multivessel disease (Maeda, 1994). In NSTEMI, 3-vessel disease and LM disease are more common with ST depression than with other ECG manifestations (Patel et al., 2014).

Among patients with NSTEMI, ST depression predicted increased mortality in a study by Kaul et al. The effect was strongest in patients with ST depression ≥2.0 mm: 30-day mortality was 3.3%, 2.9%, and 12.2% in patients with no ST depression, 1 mm ST depression, and ST depression ≥2.0 mm, respectively. One-year mortality in the respective groups was 6.7%, 8.0%, and 22.9%, $p<0.001$ in both endpoints. (Kaul et al., 2001) In a registry study of NSTEMI patients, ST depression was independently associated with in-hospital mortality. Adjusted OR for in-hospital mortality was 1.46 (95% CI 1.37-1.54) for ST depression, 1.15 (95% CI 0.97-1.37) for transient ST elevation, and 0.91 (95% CI 0.83-0.99) for TWI, compared to normal ECG. (Patel et al., 2014) In another study, four-year survival was 82% in patients with ≥0.5 mm ST depression and 94% in patients with no ST deviation ($p=0.020$). Greater ST depression resulted in worse outcomes: the survival rate was only 53% with ST depression ≥2.0 mm, 77% with 1 mm ST depression, and 82% with 0.5 mm ST depression, $p<0.0001$. (Hyde et al., 1999)

Jin et al. studied the outcome of 345 NSTEMI patients. Only patients who underwent PCI were included and those with LBBB were excluded. Thirty-day mortality was 15.7% in patients with ST depression, 2.2% with TWI, and 3.5% in the category of no ECG change, $p<0.001$. Mortality at one year was 21.0%, 8.8%, and 9.2%, respectively, $p <0.05$. (Jin et al., 2016)

2.4.2 T-wave Inversion (Without ST Elevation)

TWI in unselected patients may be caused by many conditions. TWI does not necessarily reflect ischemia or affect short-term outcomes (Walder & Spodick, 1993). However, the prevalence of coronary heart disease is higher in patients with anterior or lateral TWI, and mortality is higher in patients with lateral TWI (Istolahti et al., 2021).

As mentioned earlier, TWI in ACS may reflect a late stage of the MI process, where acute ischemia and ST changes have passed, and the myocardium has

progressed toward necrosis or reperfusion. A study by Maeda et al. comparing TWI with ST depression in non-Q-AMI showed that one-month mortality was lower with TWI (0%) than with ST depression (41%, $p<0.05$). In that study, most TWIs were preceded by ST elevation, implying that TWIs represented aborted or reperfused STEMIs. (Maeda, 1994)

During the pre-reperfusion era, UA patients with deep, anterior symmetrical TWIs were at high risk (12/16, 75%) of developing an anterior MI within weeks after the acute event (de Zwaan, Bar, & Wellens, 1982). This so-called "Wellens' sign" was found to be associated with stenosis of the LAD. In 118 consecutive patients with UA, anterior 2mm TWIs were found in 29 patients. LAD stenosis ≥70% was present in 86% of patients with anterior TWI compared to 26% of patients with no anterior TWI, $p<0.001$ (Haines, Raabe, Gundel, & Wackers, 1983).

In a registry study by Patel et al., NSTEMI patients with transient ST elevation, ST depression, or TWI were compared to patients with no ischemic changes. Unadjusted in-hospital mortality was lowest in TWI and in the multivariable model, OR for in-hospital mortality was 0.91 (95%CI 0.83-0.99) compared to no ischemic changes (Patel et al., 2014). TWI on admission was not an independent predictor of in-hospital mortality in a substudy on NSTE-ACS patients in the GRACE study and Canadian ACS Registry I. OR was 1.06 (95% CI 0.65-1.75, $p=0.81$) for resolved TWI and 0.73 (95% CI 0.48-1.11, $p=0.14$) for persistent TWI compared to no TWI (Sarak et al., 2016).

Savonitto et al. conducted a large retrospective study of 12,142 ACS patients enrolled in the GUSTO IIb study (Savonitto et al., 1999). Mortality and re-infarction were lower during the 30-day follow-up in patients with TWI (5.5%) compared to those with ST elevation (9.4%), ST depression (10.5%), or these two combined (12.4%), $p<0.001$.

T-wave abnormality (TWI, biphasic, or isoelectric T wave in leads with normally positive T waves) was strongly associated with myocardial edema in CMR in patients with NSTE-ACS (Cardona et al., 2018). Edema in T2-weighted CMR is thought to be a sign of an endangered but salvageable myocardium.

Few studies have surveyed long-term outcomes of ST depression/TWI. Hyde et al. studied 370 consecutive NSTE-ACS patients (Hyde et al., 1999). In the four-year follow-up, ST depression predicted higher mortality (30%) than TWI (16%), or normal ECG (6.1%, $p<0.05$). A Swiss study recruited consecutive NSTE-ACS patients in an observational manner (Mueller, Neumann, Perach, Perruchoud, &

Buettner, 2004). During the 36-month follow-up, mortality was 8.0% in patients with normal ECG, 19.9% with ST depression, and 5.1% with isolated TWI (p=0.0001). In the multivariable model, ST depression predicted higher (HR 2.2, 95% CI 1.1-4.6) and TWI lower (HR 0.44, 95% CI 0.20-0.96) mortality.

2.4.3 Global Ischemia

Stenosis of the LM or all three main coronary artery branches (3-vessel disease) results in widespread and severe subendocardial ischemia of the LV. This results in an ST vector toward lead aVR and widespread ST depression and TWI, most prominent in leads V4-V5. This phenomenon is called circumferential subendocardial ischemia or global ischemia (K. C. Nikus et al., 2012). The most recent ESC STEMI guidelines state that ST depression ≥1 mm in ≥8 surface leads, coupled with ST elevation in aVR and/or V1, suggests LM or LM equivalent obstruction or severe 3-vessel disease (Ibanez et al., 2018).

In a study by Sclarovsky et al., 18 of 26 patients with unstable angina and ST depression in leads V4-V5 had LM or LM equivalent disease. In the patients with precordial lead ST elevation, only two out of 20 patients had LM or LM equivalent disease. (Sclarovsky et al., 1986) Another study compared anterior ST depression associated with positive T waves to anterior ST depression with TWI (global ischemia) in patients with NSTE-ACS. Coronary angiography almost exclusively showed 3-vessel disease, LM disease or LM equivalent disease in global ischemia (76% vs. 8%, p<0.001), whereas anterior ST depression with positive T waves mostly showed one-vessel disease with the culprit lesion in the LAD or the LCx (K. C. Nikus et al., 2004). A larger sum (>6 mm - 43 mm in the highest quartile, compared to 0-2mm and 2-6mm) of ST depression in NSTE-ACS correlates with LM (p<0.0001) or 3-vessel disease (p<0.0001) (Savonitto et al., 2005). In patients with proven LM disease, the most common ECG finding was anterior ST depression in V3-V5 (maximally in V4) and ST elevation in V1 and aVR (Atie et al., 1991).

Global ischemia in the ECG results in higher in-hospital mortality (24% vs. 0%, p=0.02) than anterior ST depression with positive T waves (K. C. Nikus et al., 2004). During a 10-month follow-up, GI predicted worse outcome (composite of death, resuscitation, stroke, unstable angina or re-infarction) than all other ECG morphologies in NSTE-ACS (48% vs. 36%, p<0.001) (K. C. Nikus et al., 2012). Taglieri et al. studied the significance of ST depression with ST elevation in lead aVR compared with ST depression alone, TWI, ECG confounders, and no ST-T changes.

ST depression with ST elevation in aVR predicted CV mortality during one-year follow-up (HR 4.34, 95% CI 2.47-7.60, p<0.001 compared to normal ECG). HR for ST depression alone was 1.99 (95% CI 1.14-3.48, p=0.015. (Taglieri et al., 2011)

2.4.4 Pathological Q Waves in NSTE-ACS

The significance of Q waves was comprehensively studied during the time when MIs were classified as either Q-wave- or non-Q-AMI depending on the development of new Q waves. In unselected patients with suspected ACS, 10-year mortality was higher in patients with non-Q-AMI (70.3%) than in those who developed Q waves (60.1%, p=0.004). (Herlitz et al., 2001) Initial ST elevation was more common in the Q-wave-AMI than in the non-Q-AMI category (73% vs. 25%, p<0.0001). Initial Q waves were found in 36% and 6% in the respective groups (p<0.0001).

The significance of baseline (present at admission) pathological Q waves in NSTE-ACS has been less studied. Most studies on NSTE-ACS – even those dealing with ECG changes – mostly ignore baseline Q waves (Chen et al., 2020). In a study by Das et al., baseline Q waves were found in 23% of NSTEMI patients (Das et al., 2009). Q waves did not predict higher three-year mortality in MI (STEMI or NSTEMI) when adjusted for age, diabetes, hypertension, hypercholesterolemia, smoking, and family history of coronary artery disease (HR 1.47, 95% CI 0.96–2.25, p=0.076).

A Canadian study reported baseline Q waves in 36% of NSTE-ACS patients (Alkaabi et al., 2008). Patients with new, persistent, or normalized Q waves were compared to patients with no Q waves. There was no difference in the in-hospital (p=0.432) and one-year (p=0.485) mortality rates between these groups.

Hersi et al. found baseline Q waves in 28% of NSTE-ACS patients. They also studied Q waves at hospital discharge and investigated the outcome associated with persistent Q waves, temporary Q waves, new Q waves, and no Q waves. Six-month mortality was 4.5%, 1.9%, 5.4%, and 1.9% in the respective groups, p=0.106. Predischarge Q waves were associated with higher (4.8% vs. 1.9%, p=0.021) six-month mortality. (Hersi et al., 2003)

2.4.5 Left Ventricular Hypertrophy

LVH is a type of LV remodeling represented by pathological wall thickening and/or increase in LV mass. Higher QRS voltage is caused by larger mass of electrically active myocardium, larger LV surface area, increased LV blood volume, and close distance of the enlarged LV to the chest wall. Repolarization abnormalities in LVH are called LV strain and are reflected in the ECG as a downsloping ST segment and subsequent TWI predominantly in lateral precordial leads V5-V6. LV strain is associated with interstitial fibrosis, delayed conduction, and/or hypertrophied myocardium. (Rodrigues et al., 2017; B. Surawicz & T. Knilans, 2008)

ECG signs of LV strain are associated with perfusion abnormalities in thallium imaging, as compared to hypertensive patients without LV strain (Pringle, Macfarlane, McKillop, Lorimer, & Dunn, 1989).

QRS voltage criteria, especially the Sokolow-Lyon criteria, have long been used to diagnose LVH, but they are known to be insensitive although specific for LVH (Reichek & Devereux, 1981). Compared with echocardiography, the Sokolow-Lyon voltage criteria had 5% sensitivity and 97% specificity for LVH (J. Schroder et al., 2015). Thus, the term ECG-LVH is used in this section to distinguish from anatomical LVH detected by imaging.

The Sokolow-Lyon criteria utilize the amplitudes of the S wave in V1 and R wave in either V5 or V6. ECG-LVH is considered to be present when the sum of these waves exceeds 35 mm, or when the R-wave amplitude in lead aVL is >11 mm. In the Cornell voltage criteria, SV3 + RaVL >28 mm in men and >20 mm in women, also denotes ECG-LVH. The Cornell voltage duration product is derived from the Cornell voltage criteria and is defined as: [(RaVL + SV3) +8 mm for women] × QRS duration ≥2,440 mm ms]. Other criteria for ECG-LVH exist as well. (Okin, Roman, Devereux, & Kligfield, 1995; van Kleef et al., 2018; Williams et al., 2018)

ECG-LVH in the general population is associated with several CV risk factors. Already in 1969, the Framingham study showed a high prevalence of hypertension and high mortality among patients with ECG-LVH (Kannel, Gordon, & Offutt, 1969). In a more recent study, ECG-LVH was associated with higher blood pressure, obesity, and previous CV disease, and predicted higher CV mortality in hypertensive patients (Antikainen et al., 2006)

ECG-LVH harbors poor outcomes in NSTE-ACS. ECG-LVH was compared to no LVH in a study with NSTE-ACS patients from the GRACE and ACS-I registries

(Ali et al., 2011). The patients with ECG-LVH had more comorbidities and higher rates of in-hospital heart failure (21.8% vs 11.8%, p<0.001). In-hospital mortality did not differ between the groups, but ECG-LVH predicted higher six-month mortality (10.5% vs. 7.1%, p=0.038). When adjusted with other risk factors in the multivariable analysis, ECG-LVH was not an independent predictor of six-month mortality (OR 0.84, 95% CI 0.52-1.35, p=0.47).

The significance of ECG-LVH in assessing the outcome of NSTE-ACS patients was also studied in the GUSTO IV ACS trial (Westerhout et al., 2007). Patients with ECG-LVH were older and had more comorbidities, such as hypertension, diabetes, previous MI, or previous stroke, than patients with no ECG-LVH. ECG-LVH predicted higher 30-day mortality (5% vs. 3%, p=0.046), and at one year, ECG-LVH doubled the mortality (14% vs. 7%, p<0.001). Jn this study, the results were also alleviated when adjusted with other variables. In multivariable analysis, ECG-LVH only predicted one-year mortality in women (HR 1.42, 95% CI 1.04-1.94, p=0.029).

2.4.6 Left Bundle Branch Block

2.4.6.1 Definition

There are several definitions for LBBB in the ECG. Recent ESC guidelines define LBBB as follows (Glikson et al., 2021):

1. QRS ≥120 ms.

2. Notches or slurring in the middle third of QRS in at least two of the following leads: V1, V2, V5, V6, I, and aVL – with a prolongation at the delayed peak in R in V5-V6 to longer than 60 ms.

3. Generally, the ST segment is slightly opposed to the QRS polarity, and particularly when it is at least 140 ms and is rapidly followed by an asymmetrical T wave also of opposed polarity.

4. Horizontal plane: QS or rS in V1 with small "r" with ST slightly elevated and positive asymmetrical T wave and unique R wave in V6 with negative asymmetric T wave. When the QRS is less than 140 ms, the T wave in V6 may be positive.

5. Frontal plane: exclusive R wave in I and aVL, often with a negative asymmetrical T wave, slight ST depression, and usually QS in aVR with positive T wave.

6. The QRS axis is variable.

The AHA criteria for LBBB are quite similar (Kusumoto et al., 2019). Most LBBB criteria use a threshold of 120 ms for the QRS width. This view has been criticized by Strauss et al. (Strauss et al., 2011), who argued that the criteria for true LBBB should be stricter. The criteria proposed by Strauss et al. include QRS width ≥140 ms in men and ≥130 ms in women along with notching or slurring of the mid-QRS in at least two contiguous leads. According to Strauss et al., using less-strict criteria may lead to defining patients with no complete LBBB, such as left anterior hemiblock (LAHB) or LVH, as LBBB. In other words, some patients with IVCD could be classified as LBBB.

2.4.6.2 LBBB in Coronary Artery Disease

LBBB can be caused by various cardiac conditions, including ACS and chronic MI (Perez-Riera et al., 2019). The blood supply of the left bundle branch comes from the septal branches of LAD and the distal branches of RCA or LCX (K. Nikus et al., 2021). Hence, multivessel disease is often found in patients with LBBB and ACS, especially in new LBBB (Moreno et al., 2002; Norris & Croxson, 1970).

ACS patients with new or presumably new LBBB were earlier considered STEMI equivalents and treated accordingly. More recently, it was shown that old or presumably new LBBB did not predict MI compared to no LBBB in patients with symptoms suggestive of ACS. The rate of MI was 5.2%, 7.3%, and 6.1% in the respective groups, p= 0.75 (Chang et al., 2009). Another study found a 30% incidence of AMI among patients with chest pain and LBBB (Nestelberger et al., 2019). Moreno et al. studied patients who were considered pPCI candidates due to AMI and ST elevation or LBBB in the ECG. The study showed no difference in initial angiographic TIMI 2-3 flow between patients with and without LBBB. TIMI 2-3 flow was found in 18% of patients with LBBB and in 12% of the rest of the patients, p=0.167 (Moreno et al., 2002). The prevailing guidelines recommend treating patients with LBBB like STEMI when there is high suspicion of ongoing myocardial ischemia. Otherwise, evaluation of troponin values should be done before proceeding to coronary angiography. (Collet et al., 2020; Ibanez et al., 2018)

In a minority of patients with suspected ACS, it is possible to predict coronary artery occlusion based on the ECG findings. Sgarbossa et al. studied patients from the GUSTO-1 trial in 1996 and established criteria to predict AMI in patients with

LBBB. According to these criteria, diagnosis of AMI requires ≥1 mm ST elevation concordant with a positive QRS complex or ≥1 mm ST depression in any of leads V1-V3 (Sgarbossa et al., 1996). In a meta-analysis, the specificity of these criteria was 98% and their sensitivity was 20% (Tabas, Rodriguez, Seligman, & Goldschlager, 2008).

A third criterion used by Sgarbossa et al. was discordant ST elevation of ≥5 mm. However, this criterion was found to be insufficient for the diagnosis of AMI. Smith et al refined this criterion in their study. Instead of using an absolute ST elevation of ≥5 mm, they used proportional ST elevation compared to the preceding S wave. ST elevation ≥ 25% of the depth of the preceding S wave along with the Sgarbossa criteria (≥1 mm concordant ST elevation or ≥1 mm concordant ST depression in V1-V3) yielded 91% sensitivity and 90% specificity (Smith, Dodd, Henry, Dvorak, & Pearce, 2012). These criteria are referred to as "Smith criteria" or "modified Sgarbossa criteria."

Recently, a Spanish group introduced the BARCELONA algorithm, which theoretically could improve the prediction of AMI in LBBB patients with leads showing low-amplitude QRS (Di Marco et al., 2020). This algorithm defines STEMI as ≥1 mm concordant ST deviation in any lead or ≥1 mm discordant ST deviation in any lead with maximum deflection (R or S) ≤6 mm. The sensitivity was 93% in the BARCELONA criteria, 33% in the Sgarbossa criteria ($p<0.01$ for the difference), and 68% in the Smith criteria ($p<0.01$). The specificity was 94%, 99% ($p=0.08$), and 94% ($p>0.99$) in the respective groups. The BARCELONA criteria still need to be validated in larger populations.

2.4.6.3 Prognosis

Many publications have dealt with the prognostic role of LBBB in ACS. In a study published in 1970, Norris et al. reported a mortality rate of 48% in patients with LBBB admitted to the coronary care unit (Norris & Croxson, 1970). Mortality of RBBB was even higher (61%).

LBBB has also predicted poor outcome in later publications. A large registry study on patients with AMI showed higher in-hospital mortality in LBBB (22.6%) and RBBB (23.0%) than in no BBB (13.1%, $p<0.001$) (Go, Barron, Rundle, Ornato, & Avins, 1998). In AMI patients (STEMI or LBBB) treated with pPCI, LBBB

predicted higher in-hospital mortality compared with ST elevation (41% vs. 11%, p=0.002) (Moreno et al., 2002).

The ASSENT 2 and 3 trials enrolled patients with recent-onset (<6 hours) symptoms of AMI and either ST elevation (n=22 572) or presumably new LBBB (n=267). Mortality at 30 days was higher in patients with LBBB (13.5%) than in those with STEMI without LBBB (6%). One-year mortality was 25.2% in LBBB and 9.1% in STEMI. The patients who fulfilled the Sgarbossa criteria had higher mortality than other patients with LBBB and patients with no LBBB, both at 30 days (23.5% vs. 7.7% vs. 6.0%, respectively, p<0.001) and at one year (33.7% vs. 20.2% vs. 9.1%, p<0.001). (Al-Faleh et al., 2006)

In a study on UA and non-Q-AMI, patients with LBBB had the highest one-year mortality (18.2%) as compared to ST deviation ≥1mm (9.8%), isolated T-wave changes (5.6%), or no ECG changes (5.5%), p<0.001. LBBB predicted one-year mortality in the multivariable analysis (RR 2.80, 95% CI 1.81-4.32, p<0.001) (Cannon et al., 1997).

A meta-analysis compared new LBBB to other AMIs and found higher risk of death at 30 days (OR 2.10, 95% CI 1.27-3.48) and at one year (OR 2.81, 95% CI 1.64-4.80) (Al Rajoub et al., 2017).

Hyde et al. studied consecutive patients with NSTE-ACS (Hyde et al., 1999). In their four-year follow-up study, patients with LBBB had 45% mortality, compared to 30% in ST depression, 16% in TWI, and 6.1% in no ECG changes (p value not reported). LBBB predicted four-year mortality in the univariate analysis (p=0.02, OR not reported) but not in the multivariable analysis.

2.4.7 RBBB in ACS

Poor outcome of RBBB was originally reported decades ago. Norris et al. in 1970 reported a mortality rate of 61% in patients with RBBB who were admitted to the coronary care unit (Norris & Croxson, 1970). The mortality rate was higher in patients with RBBB than in those with LBBB.

RBBB has mostly been studied in patients with STEMI or unselected ACS. Chan et al. found no difference between the different ACS categories regarding in-hospital or six-month mortality (Chan et al., 2016). However, in-hospital mortality was 8.8% in ACS with RBBB and 3.8% in ACS without RBBB (p<0.001), and six-month

mortality was roughly twice as high with RBBB (15.1% vs. 7.6%, p<0.001). After adjusting with components of the GRACE risk score, RBBB still predicted in-hospital (OR 1.45 95% CI 1.02-2.07, p=0.039) but not six-month mortality (OR 1.29 95% CI 0.95-1.74, p=0.098).

In unselected patients with suspected AMI, one-year mortality in RBBB was 10.7% and 7% in LBBB (Neumann et al., 2019). After adjustment, LBBB (HR 1.71, 95% CI 1.17-2.50, p=0.0055) but not RBBB (HR 1.29, 95% CI 0.71-2.34, p=0.40) was significantly associated with one-year mortality. STEMI was diagnosed in 4.8% of patients with RBBB on admission.

There is little data on outcomes of RBBB in NSTE-ACS specifically. A study by Kleemann et al. compared the prognostic significance of RBBB in NSTEMI and STEMI (Kleemann et al., 2008). Unlike in STEMI, where the peak cardiac enzyme levels were higher and left ventricular ejection fraction values lower in patients with RBBB than in those without RBBB, no significant differences were detected in NSTEMI patients with and without RBBB. Unadjusted in-hospital mortality was higher in NSTEMI patients with RBBB than in those without (8.1% vs 4.9%, p=0.003). However, there was no independent association between RBBB and in-hospital or long-term mortality in NSTEMI.

Bansilal et al. studied patients with a first episode of angina (ST elevation excluded) (Bansilal et al., 2011). In the seven-year follow-up, mortality was 46.0% in RBBB, 65.8% in LBBB, and 27.2% in no BBB, p<0.001.

2.4.8 Other ECG Categories and Outcomes

Recently, many new ECG manifestations have been introduced for the assessment of outcome in NSTE-ACS. The V-index is a computed metric measuring the spatial heterogeneity of ventricular repolarization. The index predicted an NSTEMI diagnosis among patients with chest pain and was also an independent predictor of two-year mortality among patients with suspected NSTEMI (Abacherli et al., 2017).

Fragmented QRS (fQRS) is defined as notching of the R wave and/or S wave in at least two contiguous leads in major coronary territories in the absence of BBB. fQRS was an independent predictor of mortality in ACS in a mean follow-up of 34 months (HR 1.68, 95% CI 1.89–2.38, p=0.003). The study was retrospective, and consecutive patients who had undergone cardiac catheterization were included. (Das et al., 2009)

The QRS-T angle can be automatically computed from the ECG. It is altered in myocardial ischemia due to depolarization-repolarization heterogeneity in the ischemic myocardium. A wider QRS-T angle predicted an NSTEMI diagnosis over other causes of chest pain among patients with suspected NSTEMI. An increase of 10° in the QRS-T angle predicted two-year mortality in univariate (HR 1.32, 95% CI 1.26-1.40, p<0.001) and multivariable analysis (HR 1.05, 95% CI 1.01-1.09, p=0.019). (Strebel et al., 2019)

2.4.9 Comparison of Different ECG Findings in NSTEMI

There is little data on the relation of different ECG findings in NSTE-ACS. Schmitz et al. studied 9,689 patients with a first AMI. Only patients who had survived the first 28 days and whose relevant data were available were included. Long-term mortality of ST depression, TWI, unspecific changes, normal ECG, and BBB were compared to STEMI. During the median follow-up of 6.7 years, mortality was 27.5% in STEMI, 47.6% in ST depression, 36.0% in TWI, 33.4% in unspecific changes, 20.9% in normal ECG, and 52.8% in BBB. The Kaplan-Meier analysis showed the lowest survival in BBB, followed by ST depression, unspecific changes and TWI with overlapping curves, STEMI, and finally normal ECG. Compared with STEMI in the age- and sex-adjusted Cox regression analysis, normal ECG predicted lower mortality (HR 0.74, 95% CI 0.64–0.85, p<0.001). In contrast, ST depression (HR 1.58, 95% CI 1.42–1.76, p<0.001), TWI (HR 1.20, 95% CI 1.07–1.34, p=0.001), unspecific changes (HR 1.27, 95% CI 1.15–1.41, p<0001), and BBB (HR 1.95, 95% CI 1.73–2.21, p<0.001) predicted higher mortality. (Schmitz et al., 2022)

2.5 Future Aspects in ECG and Myocardial Ischemia

Machine learning and artificial intelligence are potential tools for radical changes in ECG interpretation, as computers can give accurate predictions from subtle ECG signals invisible to the human eye. This is already happening, although it may take some years until eyeballing is replaced with computer analysis in everyday clinical practice.

In a study by Al-Zaiti et al., machine learning was used to assess the probability of AMI according to 554 temporal-spatial features in the ECG. Patients with confirmed STEMI were excluded. Sensitivity and specificity for myocardial ischemia were 0.72 (0.60–0.81) and 0.76 (0.72–0.80) in the machine learning model. The

respective numbers were 0.26 (0.16–0.37) and 0.94 (0.92–0.96) for experienced clinicians and 0.12 (0.06–0.22) and 0.98 (0.97–0.99) for commercial interpretation software. (Al-Zaiti et al., 2020)

3 AIMS OF THE STUDY

The aims of the present study were:

- To study the mid-term mortality of STEMI patients with ischemia grade 2 and 3
- To assess the outcome of patients with STEMI when ischemia grading does not apply
- To study the prognostic impact of Q wave and TWI in patients with STEMI
- To assess demographic aspects of ACS patients
- To assess long-term mortality in all ACSs according to ECG parameters.

4 MATERIALS AND METHODS

4.1 Study Population

4.1.1 Studies I and II

The data of Studies I and II were derived from two Finnish STEMI studies: the HUS-STEMI study and the STEMI 2005 study. The case report form was nearly identical, enabling the combination of data of the two studies. The inclusion criteria were identical for both studies, and neither had any pre-specified exclusion criteria. The inclusion criteria were as follows:

Acute chest pain/discomfort and

1) ST elevations of ≥ 2 mm in at least two of leads V1-3 and/or

2) ST elevations of ≥ 1 mm in at least two other contiguous leads (V4-6; I, aVL; II, III, aVF) or

3) new or presumably new LBBB.

The total number of patients in the combined dataset was 758 (448 in HUS-STEMI and 310 in STEMI 2005). We excluded 83 patients due to missing or invalid ECGs. In 25 patients the primary ECG was missing. In 12 patients we found the primary ECG technically non-interpretable. In 46 patients the ECG lacked ST elevation diagnostic for STEMI, although they had been included in the study by the on-site investigators. In Study II, 52 patients were excluded due to QRS >120ms. The final study population comprised 675 patients in Study I and 627 patients in Study II.

Mortality at one year was the primary endpoint. Mortality data were gathered from the official national database.

4.1.1.1 HUS-STEMI

The HUS-STEMI study took place in the hospital district of Helsinki and Uusimaa covered by the Helsinki University Hospital. Patients were recruited during one year (2007-2008). Consecutive STEMI patients were prospectively recruited. Data on pre-existent disease and other baseline characteristics were gathered as well as data related to the hospital stay, such as treatment delays and therapeutic measures received by the patient. HUS-STEMI was an observational study, and the treatment choices were made by the treating doctor according to the national and local guidelines. A study nurse contacted the study patients one year after the initial admission to gather follow-up data.

4.1.1.2 STEMI 2005

The patients of the STEMI 2005 study were recruited in the hospital district of Pirkanmaa, covered by the Tampere University Hospital, and an uptake area of three central hospitals of the Tampere University Hospital region. There was a study nurse in each hospital, and a coordinating study nurse in the Tampere University Hospital. The recruitment lasted six months in 2005, and all consecutive patients with STEMI were prospectively recruited. Data gathered in this study were comparable to those in the HUS-STEMI study. STEMI 2005 was an observational study.

4.1.2 Study III (TACOS Study)

Study III dealt with long-term prognosis of the patients of the Tampere Acute COronary Syndrome (TACOS) study. All consecutive patients admitted to the Tampere University Hospital and with confirmed AMI were recruited from January 1, 2002 to March 31, 2003. Confirmed MI was defined as symptoms indicating MI and elevated blood troponin level (cTnI>0.2 μg/L). In addition, patients with negative cTnI but with symptoms indicating UA were recruited from September 1, 2002 to March 31, 2003. Only patients who survived to be admitted to hospital were included. Patients discharged from the emergency department were excluded.

The total number of recruited patients was 1,188. The initial diagnosis was STEMI in 343 patients, NSTEMI in 655 patients, and UA in 190 patients. After re-analyses of the ECGs, four patients were excluded due to missing ECG (n=1) or heart rate >130 bpm (n=3). The final population in Study III comprised 1,184

patients. Follow-up of the survivors ended on 31 January 2013. The median follow-up time was 10.3 years for the patients who survived. As in Studies I and II, mortality data were gathered from the official national database.

4.2 ECG Definitions

A 12-lead ECG was available for all study patients. The availability of supplemental ECG leads (V3R, V4R, V7-9) varied. Most ECG parameters used in this study have been validated on the basis of a 12-lead ECG recording. Consequently, supplemental leads were not used in the analyses. All ECGs in Studies I and II were analyzed by the author of this thesis. In case of ambiguity, consensus was sought with two experienced senior cardiologists. In Study III, all ECGs were analyzed by two senior cardiologists. ECGs with reported ST elevation, LBBB, or other ECG changes were re-analyzed by the author of this thesis as described above.

4.2.1 ST Elevation

ST elevation was defined in Studies I and II according to the criteria mentioned in section 4.1.1.

In Study III, a contemporary definition for STEMI was used:

- ST elevation in two adjacent leads
- ≥1.5 mm in leads V1-V6 with at least 2 mm in at least one lead
- ≥1 mm in leads aVL, I, II, aVF, and III

In RBBB, the standard criteria for ST elevation were applied

4.2.2 Grades of Ischemia

We defined G2I and G3I according to the refined criteria by Billgren et al. (Billgren et al., 2004). We did not include grade 1 ischemia, as by definition, this ECG pattern represents ischemia without ST elevation. G3I was defined as distortion of the terminal portion of the QRS complex, defined as follows:

- in a qR type complex, J point at or above 50% of the height of the R wave
- in an rS type complex, disappearance of the S wave, or the lowest part of the S wave above the baseline

G2I was defined as STEMI without terminal QRS distortion as defined above (Figures 1 and 2).

Study I included a STEMI patient category, where ischemia grading did not apply: patients with a broad QRS complex (>120 ms) or any TWI (at least -0.5 mm) in the leads with maximal ST elevation are excluded from ischemia grading. We constructed a "No grade" (NG) group to include these patients. An example of an ECG classified as NG is shown in Figure 3.

Presence of Q waves was no hindrance for ischemia grading. QS complex followed by STE was usually interpreted as G2I.

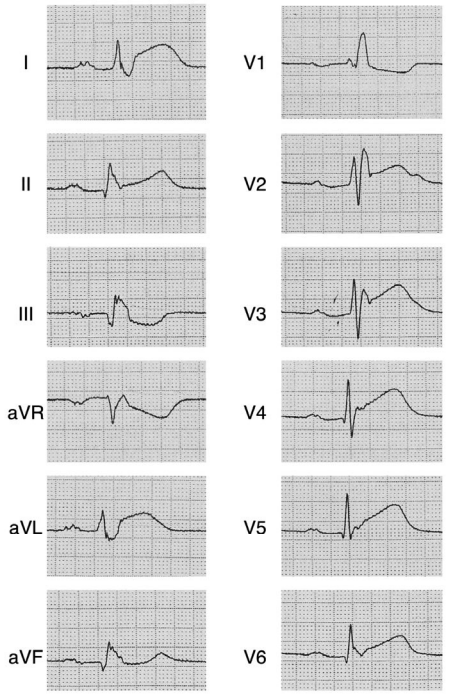

Figure 3. An ECG classified as "No grade" due to broad QRS (RBBB).

4.2.3 Q Waves

The Fourth Universal Definition of Myocardial Infarction defines the criteria for pathological Q waves (Thygesen et al., 2018). These criteria were mentioned in section 2.3 and were utilized in Studies I and II. At the time of writing these articles, the Third Universal Definition of Myocardial Infarction was cited. However, the criteria for pathological Q waves remained intact in the Fourth Universal Definition of Myocardial Infarction. In Study II, only Q waves in leads with maximal ST elevation were taken into account, as remote Q waves were considered less likely to be related to the ongoing ischemic process.

In Study III, Q waves were defined according to the contemporary definition:

- any Q wave at least 30 ms in leads V1-V3
- Q wave at least 1 mm in height and at least 30 ms in at least two adjacent leads in leads I, II, aVL, aVF, V4-V6
- in leads V1-V2, R wave >40 ms and R/S ratio >1 in the absence of pre-excitation, right ventricular hypertrophy, or RBBB

In Study II, four ECG categories were formed according to the presence of Q waves and/or TWI. An example of each category is shown in Figure 4.

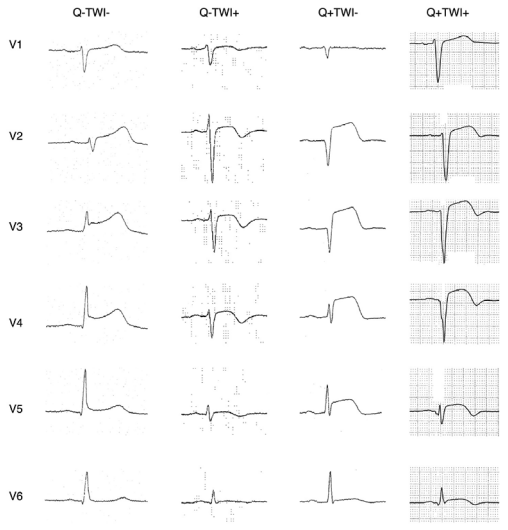

Figure 4. The four ECG categories used in Study II.

4.2.4 T-wave Inversion and ST Depression

There is no universally accepted definition of TWI. For example, the Fourth Universal Definition of Myocardial Infarction mentions TWI as an example of ischemic findings in the ECG, but no cut-off for pathological TWI is given (Thygesen et al., 2018). We used a cut-off -0.5 mm. The T wave was considered inverted if at least part of it reached -0.5 mm.

As in TWI, there is no universally accepted definition for pathological ST depression. In Study III, we used a cut-off of -0.5mm measured at the J point.

As ST depression and TWI often are seen simultaneously, patients with ST depression and/or TWI were combined to form a separate category in Study III.

4.2.5 Global Ischemia

Global ischemia was defined as ST depression of at least -0.5 mm in at least six leads, maximally in leads V4-V5 combined with inverted T waves and reciprocal ST elevation in lead aVR of at least 0.5 mm.

4.2.6 Left Ventricular Hypertrophy

We used the Sokolow-Lyon voltage criteria for the diagnosis of ECG-LVH. These criteria were met when the S wave in lead V1 + the R wave in lead V5 or V6 was 35 mm or more AND/OR the R wave in lead aVL was >11 mm. We studied the electrical phenomenon of ECG-LVH rather than true LVH as the sensitivity of ECG-LVH for true LVH is known to be low, as mentioned earlier.

4.2.7 Left Bundle Branch Block

We defined LBBB as follows:

- QRS ≥120 ms
- peak of the R wave at >60 ms in leads V5-V6
- broad and notched or slurred R waves in leads aVL, V5 and V6
- Q waves absent in leads I, V5, and V6

This definition follows the definition by the ESC cited in section 2.4.

4.2.8 Right Bundle Branch Block

Our definition for RBBB was (Surawicz et al., 2009):

- QRS ≥120 ms
- rsr´, rsR´ or rSR´ configuration in lead V1 or V2 OR, in the presence of pure dominant R wave in V1, normal R-peak time in V5-V6 but >50 ms in V1
- S-wave duration > R-wave duration and >40 ms in leads I and V6

4.2.9 Other ECG Changes

In Study III, the patients who did not fulfill the criteria for any group listed above formed the group "Other ECG changes." This group consisted of patients with intraventricular conduction defects (n=36), ventricular paced rhythm (n=18), other ventricular rhythm (n=4), ST changes that did not fulfill the criteria for ST elevation or ST depression (n=3), tall T waves (n=3), pre-excitation (n=1), and extreme left axis deviation (n=1).

4.2.10 Simultaneous ECG Findings

In Study III, many patients had two or more simultaneous ECG changes. Therefore, the classification was based on the following hierarchy: LBBB > ST elevation > RBBB > GI > LVH > ST depression/TWI > Q wave. Thus, patients with simultaneous ST depression/TWI and Q wave were classified as ST depression/TWI.

4.3 Statistical Methods

All statistical analyses were performed using SPSS (IBM Corporation, USA) software. In each study, the latest version of the SPSS software was used. In Study I, we used SPSS 22, and in Studies II and III, SPSS 25.

We compared baseline characteristics and outcome in the different ECG groups in each study. In Study I, the groups were G2I, G3I, and "No grade"; in Study II, Q+TWI+, Q-TWI+, Q+TWI-, and Q-TWI-; in Study III, normal ECG, ST elevation, ST depression/TWI, RBBB, Q wave, global ischemia, LVH, LBBB, and "Other ECG changes."

To compare categorical variables, we used the chi square test, and when necessary (due to low numbers of cases), Fisher´s exact test. The continuous variables were skewed in each dataset, and we therefore presented median values with interquartile ranges. For continuous variables, we used the Mann-Whitney U test (two groups) or Kruskal-Wallis test (three or more groups) to test the difference between the groups.

We presented Kaplan-Meier curves to study the survival of the participants. Log-Rank test was used to test the difference of survival between the different ECG groups.

We performed binary logistic regression analysis to study the risk of death of the patients in the different ECG groups. In Studies I and II, we used one-year mortality as the endpoint. We presented odds ratios with 95% confidence intervals. After the univariate analysis, we included the variables with $p<0.1$ to the multivariable analysis.

In Study III, death during the 10-year follow-up was the endpoint in the Cox regression analyses. We presented hazard ratios with 95% confidence intervals. We only used ECG groups, age, and gender in the multivariable model. This decision is discussed in Chapter 6.

4.4 Ethical Aspects

The studies of this thesis are based on three clinical studies described above: the HUS-STEMI, STEMI 2005, and TACOS studies. The ethical protocol was similar in all three studies. All patients signed written informed consent before enrolment. The studies were observational, and the patients were treated according to the national and local guidelines. Thus, consent was given basically to use the patient data for scientific purposes. Participation in the studies did not affect the treatment received by the patients.

The local ethical committees approved the protocols of each study. The studies were carried out according to the principles of the Declaration of Helsinki.

5 SUMMARY OF THE RESULTS

5.1 Patient Characteristics in the Different ECG Groups

5.1.1 Baseline Characteristics of STEMI Patients with Different Grades of Ischemia

In Study I, we studied STEMI patients with G2I and G3I and those STEMI patients to whom ischemia grading did not apply. Baseline characteristics of the patients in each category are shown in Table 2. G2I was the most common group (n=458). "No grade" (NG) (n=135) and G3I (n=86) were less common. The proportion of G3I was 15.8% of the patients in whom ischemia grading was applicable, and 12.7% of all STEMIs. In this chapter, all p values reflect the difference between all three groups (NG, G2I, and G3I).

Median age did not differ between the three groups (p=0.267). There was overrepresentation of males in all groups: 62.6% in NG, 64.4% in G2I, and 74.4% in G3I, p=0.154.

Distribution of different baseline characteristics was mostly similar between G2I and G3I. Congestive heart failure was more common in G2I (5.2%) than in G3I (1.2%). Of patients with G3I, 1.2% had undergone prior CABG, and this proportion was 2.1% in G2I. In G2I, 26.1% of the patients had Killip class >1, whereas 32.9% of G3I patients belonged to this category of acute heart failure. Pathological Q waves were found in 38.4% of G3I patients and in 20.3% of G2I patients.

The baseline characteristics of the patients with no grade of ischemia differed from those of G2I and G3I in many ways. Prior congestive heart failure was most common in NG (12.4% vs. 5.2% in G2I, and 1.2% in G3I, p=0.001). Baseline renal insufficiency was found in 6.9% of the NG patients, this proportion being 2.4% in G2I, and 3.5% in G3I, p=0.045. Use of ACEi/ARB was more common in NG than in G2I or G3I (34.6%, 23.9%, and 22.4%, respectively), p for the difference was 0.036.

The NG group stood out in receiving least often immediate reperfusion therapy. The rate of no immediate reperfusion therapy was 25.2% in NG, 9.6% in G2I, and 8.1% in G3I, $p<0.001$. FT was administered least often in NG (32.1%). A total of 62.8% of the G3I patients and 56.8% of the G2I patients received FT, $p<0.001$. There was no statistically significant difference in the rate of pPCI between the NG, G2I, and G3I groups (42.7% vs. 33.6% vs. 29.1%, respectively, $p=0.075$).

Time from symptom onset to ECG was more than double (172 min) in the NG group compared with the G2I (80 min) and G3I (75 min) groups, $p<0.001$, while time from symptom onset to treatment was 286 min, 150 min, and 110 min in the respective groups, $p<0.001$.

Table 2. Baseline characteristics based on ECG ischemia grading.

	NG		G2I		G3I		
	Median	**Quartiles**	**Median**	**Quartiles**	**Median**	**Quartiles**	**p value**
Age (years)	69.5	58.9-78.6	65.5	56.7-76.0	66.8	55.3-76.8	0.267
Time from symptom onset to ECG (minutes)	172	69.0-380	80.0	41.0-172	75.0	42.3-182	<0.001
Time from symptom onset to treatment (minutes)	286	144-556	150	91.0-248	110	72.0-215	<0.001
	NG	**n=131**	**G2I**	**n=458**	**G3I**	**n=86**	
	%	**n**	**%**	**n**	**%**	**n**	**p value**
Male	62.6	82	64.4	295	74.4	64	0.154
Current smoker	29.4	35	37.1	161	36.3	29	0.297
Diabetes	25.2	33	17.1	78	18.6	16	0.108
Hyperlipidemia	40.5	53	47.4	217	39.5	34	0.204
Hypertension	56.9	74	56.3	258	47.7	41	0.307
Prior STEMI	16.3	21	9.9	45	8.2	7	0.082
Prior angina	31.1	37	27.6	121	28.4	23	0.750
Prior CHF	12.4	16	5.2	24	1.2	1	0.001
Prior TIA/stroke	11.5	15	7.2	33	7.0	6	0.268
Renal insufficiency	6.9	9	2.4	11	3.5	3	0.045
Prior PCI	9.2	12	5.5	25	7.0	6	0.301
Prior CABG	10.7	14	2.6	12	1.2	1	<0.001
Killip class >1	46.6	61	26.1	119	32.9	28	<0.001
Pathological Q-waves			20.3	93	38.4	33	

STEMI in anterior location			45.6	209	46.5	40	
ASA	36.2	47	28.4	130	23.5	20	0.105
Clopidogrel	3.1	4	0.9	4	1.2	1	0.153
Warfarin	6.2	8	5.2	24	3.5	3	0.686
β blocker	38.5	50	31.9	146	24.1	20	0.088
Calcium channel blocker	20.0	26	16.6	76	12.9	11	0.392
Statin	24.8	32	19.9	91	16.3	14	0.283
ACEi/ARB	34.6	45	23.9	109	22.4	19	0.036
pPCI	42.7	56	33.6	154	29.1	25	0.075
FT	32.1	42	56.8	260	62.8	54	<0.001
NRT	25.2	33	9.6	44	8.1	7	<0.001

STEMI = ST-elevation myocardial infarction, CHF = congestive heart failure, TIA = transient ischemic attack, PCI = percutaneous coronary intervention, pPCI = primary PCI, CABG = Coronary artery bypass graft, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, FT = fibrinolytic therapy, NRT = No reperfusion therapy within 4 hours from presentation

5.1.2 Baseline Characteristics of STEMI Patients with Q Waves and/or T-wave Inversions

In Study II, we compared STEMI patients with Q waves and/or TWI with those with neither of these ECG parameters. The patients without any of the studied features (Q-TWI-) was the most common group (n=418), followed by Q+TWI- (n=130), Q-TWI+ (n=50), and Q+TWI+ (n=29). Table 3 shows the baseline characteristics of the four categories.

Median age was similar among the groups. Time delays from symptom onset to ECG and to treatment were longest in the groups with TWI, $p<0.001$ for both variables.

Males were overrepresented (65.3%-82.8%) in all other groups than Q-TWI+, $p=0.003$. Diabetes was most common in the Q+TWI+ group (34.5% compared to 15.6%-22.3% of the other groups, $p=0.033$) whereas distribution of other risk factors and medications was similar among the groups.

Acute heart failure defined as Killip class >1 was most common in the groups with Q waves ($p=0.001$). Anterior STEMI was most prevalent in the Q+TWI- group (76.9%) and least prevalent in Q-TWI- group (35.9%), $p<0.001$.

There was no difference between the groups regarding the proportion of patients treated with pPCI. However, FT was more common in the groups with no TWI (55.4% and 58.4%) than in those with TWI (24.1% and 28.0%, $p<0.001$). Patients of the Q+TWI+ group were most often left without immediate reperfusion therapy (34.5%) and this percentage was lowest in the Q-TWI- group (8.4%, $p<0.001$).

Table 3. Baseline characteristics of the patients in Study II.

	Q+ TWI+ n=29 Median (quartiles)	Q- TWI+ n=50 Median (quartiles)	Q+ TWI- n=130 Median (quartiles)	Q- TWI- n=418 Median (quartiles)	p value
Age (years)	65 (54-72)	68 (58-77)	65 (55-78)	66 (57-76)	0.831
Time from symptom onset to ECG (minutes)	356 (80-730)	184 (72-465)	89 (45-208)	73 (40-161)	<0.001
Time from symptom onset to treatment (minutes)	498 (285-940)	320 (235-795)	153 (94-299)	142 (85-240)	<0.001
	Q+ TWI+ n (%)	**Q- TWI+ n (%)**	**Q+ TWI- n (%)**	**Q- TWI- n (%)**	**p value**
Gender (male)	24 (82.8)	22 (44.0)	88 (67.7)	273 (65.3)	0.003
Current smoker	14 (51.9)	13 (28.3)	44 (37.6)	148 (37.0)	0.254
Diabetes	10 (34.5)	10 (20.0)	29 (22.3)	65 (15.6)	0.033
Hyperlipidemia	11 (37.9)	15 (30.0)	64 (49.2)	188 (45.0)	0.113
Hypertension	16 (57.1)	22 (44.0)	79 (60.8)	223 (53.3)	0.206
Prior STEMI	5 (17.2)	3 (6.0)	18 (14.1)	35 (8.4)	0.093
Prior angina	10 (35.7)	14 (31.8)	30 (25.2)	115 (28.5)	0.663
Prior CHF	2 (7.1)	4 (8.0)	6 (4.6)	20 (4.8)	0.591
Prior TIA/stroke	2 (6.9)	4 (8.0)	7 (5.4)	32 (7.7)	0.846
Renal insufficiency	2 (6.9)	2 (4.0)	3 (2.3)	11 (2.6)	0.387
Prior PCI	1 (3.4)	5 (10.0)	9 (6.9)	22 (5.3)	0.461
Prior CABG	2 (6.9)	2 (4.0)	2 (1.5)	12 (2.9)	0.264
Killip class >1	13 (44.8)	15 (30.0)	51 (39.5)	99 (23.8)	0.001
STEMI in anterior location	16 (55.2)	23 (46.0)	100 (76.9)	150 (35.9)	<0.001

pPCI	12 (41.4)	24 (48.0)	41 (31.5)	139 (33.3)	0.143
FT	7 (24.1)	14 (28.0)	72 (55.4)	244 (58.4)	<0.001
NRT	10 (34.5)	12 (24.0)	17 (13.1)	35 (8.4)	<0.001
Aspirin	11 (37.9)	13 (26.0)	45 (34.6)	105 (25.2)	0.112
Clopidogrel	1 (3.4)	1 (2.0)	2 (1.5)	3 (0.7)	0.188
Warfarin	0 (0.0)	3 (6.0)	5 (3.8)	23 (5.5)	0.625
β blocker	7 (24.1)	19 (38.0)	45 (34.9)	122 (29.3)	0.356
Calcium channel blocker	3 (10.3)	11 (22.0)	22 (16.9)	66 (15.8)	0.578
Statin	9 (31.0)	7 (14.0)	27 (20.8)	79 (18.9)	0.301
ACEi/ARB	11 (37.9)	15 (30.0)	35 (26.9)	93 (22.4)	0.172

STEMI=ST-elevation myocardial infarction; CHF=congestive heart failure; TIA=transient ischemic attack; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft; pPCI=primary PCI; FT=fibrinolytic therapy; NRT=no reperfusion therapy; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker

5.1.3 Baseline Characteristics of ACS Patients with Different ECG Findings

In Study III, we compared long-term outcomes of ACS patients based on nine different ECG morphologies. These ECG groups were normal ECG (n=40), ST elevation (n=353), ST depression/TWI (n=160), global ischemia (n=97), Q wave (n=272), LBBB (n=71), RBBB (n=43), LVH (n=82), and other ECG changes (n=66). The median age of the study population was 72 years, and 41.6% of the study patients were female. The baseline characteristics of these groups are shown in Table 4.

Patients with normal ECG were younger than patients in the other groups. The median age was 60 years. The median creatinine level was 74 μmol/l and median CRP 4 mg/l, being the lowest of the groups. The proportion of females (35.0%) was lower than in most groups. Hypertension (45.0%) was less prevalent than in other groups. Type 2 diabetes (15.0%) and prior AMI (10.0%) were least common in this group. Only 45.0% of the patients with normal ECG were troponin-positive. Smoking (21.6%) was more common than in most groups. Patients with normal ECG had the lowest use of diuretics, ACE inhibitors, digoxin, and warfarin.

The median age of the patients with ST elevation (68 years) was lower than the average. Females were underrepresented in this group (36.3%). Prior AMI (15.2%) was less common than in most groups. The STE group had the highest proportion of smokers (24.9%). STE patients were often TnI positive (91.8%). In-hospital PCI took place more often (24.6%) than in the other groups. Use of β blockers, statins, ASA, and nitrates was lowest in the STE group.

The median age of the patients with ST depression and/or T-wave inversion was 72 years, which was the median age of the whole study population as well. In the STD/TWI group, 51.9% of the patients were female. Prevalence of smoking was higher (20.0%) than in most groups (18.9% in the whole population). The proportion of patients who underwent PCI (10.6%) or CABG (6.3%) was lower than in the whole study population (14.5% and 9.4%, respectively). TnI positivity (70.6%) was less common than in the whole study (84.0% in all). Only patients with normal ECG had lower percentage of TnI positivity (45.0%) than STD/TWI. Use of different medications was neither highest nor lowest in the STD/TWI group.

Patients with global ischemia were among the oldest in this study. The median age was 77 years. This group also had the highest proportion of females (56.7%). Patients with GI stood out as the ECG group with the highest prevalence of

hypertension (62.5%) and the highest percentage of TnI positivity (99.0%). Prevalence of type 2 diabetes (30.2%) and prior AMI (30.9%) were higher than in most groups. 27.8% of the GI patients underwent CABG. This was the highest proportion of all groups. Use of β blockers and nitrate was most common in GI patients. At discharge, GI patients most often used β blockers, diuretics, and nitrate.

The median age of patients with baseline Q waves was close to the study population median (73 years vs. 72 years, respectively). This ECG group had the lowest proportion of females (33.5%) and 34.8% of these patients had history of prior AMI. Only patients in the group "other" had higher percentage (38.5%) and 86% of the patients with Q waves were troponin-positive (84% in all).

LBBB patients had the highest median age (77 years) along with GI, RBBB, and LVH. The median creatinine level (100 μmol/l) was higher than in all other groups except for the group "other" (103 μmol/l). 52.1% of the LBBB patients were female. Prevalence of hypertension (59.2%) and type 2 diabetes (31.4%) were higher than in most ECG groups. There were fewer smokers (5.1%) than in any other group. The proportion of patients who underwent PCI was lowest of all ECG groups (4.2%) and 84.5% of these patients were TnI positive. Use of diuretics, ACE inhibitors, nitrate, digoxin, and warfarin was above the study average. The discharge medication of the LBBB patients showed the highest percentage of ACE inhibitors and warfarin. In contrast, clopidogrel use at discharge was lowest in the LBBB group.

The median age of the RBBB patients was 77 years and 34.9% of these patients were female. Smoking was less common in the RBBB group than in the whole study (7.7% vs. 18.9%, respectively). Prevalence of type 2 diabetes was highest in RBBB (34.9%). Prevalence of hypertension was 45.2%, the second lowest percentage after normal ECG (45.0%). At discharge, RBBB patients had the lowest use of statins.

The median age in the LVH group was 77 years, and 52.4% of these patients were female. Prevalence of hypertension (62.2%) was second highest after GI (62.5%). Median systolic blood pressure was highest of all ECG groups (160 mmHg). Use of digoxin was most common in this group. At discharge, use of angiotensin receptor blockers and digoxin were more common than in the other groups.

The ECG group with other ECG changes had median age of 75 years and 37.6% were female. They had the highest rate of prior AMI (38.5%). Prevalence of hypertension (62.1%) and type 2 diabetes (34.8%) were above the study average. This group had the lowest rate of CABG (3.0%). Patients with other ECG changes

had the highest use of statins, ACE inhibitors, ASA, and warfarin. At discharge, these patients had the lowest use of β blockers and ASA.

Table 4. Baseline characteristics of the different ECG categories in Study III.

	Normal ECG median (IQR)	ST elevation median (IQR)	STD/TWI median (IQR)	Global ischemia median (IQR)	Q wave median (IQR)	LBBB median (IQR)	RBBB median (IQR)	LVH median (IQR)	Other ECG change median (IQR)	p value
Age	60 (53-69)	68 (56-77)	72 (59-79)	77 (72-82)	73 (64-80)	77 (71-84)	77 (71-83)	77 (71-84)	75 (69-79)	<0.001
Creatinine	74 (67-95)	84 (71-99)	81 (67-99)	92 (75-115)	90 (75-112)	100 (81-127)	84 (73-114)	90 (71-120)	103 (85-135)	<0.001
Maximum CRP	4 (2-9)	10 (3-37)	9 (2-50)	19 (4-67)	22 (5-69)	14 (5-67)	13 (4-100)	16 (4-68)	11 (3-33)	<0.001
Systolic BP	145 (133-168)	144 (126-166)	150 (132-172)	144 (122-170)	141 (121-161)	146 (124-160)	156 (137-187)	160 (143-189)	139 (117-163)	<0.001
Diastolic BP	84 (71-91)	80 (70-91)	80 (70-90)	77 (62-91)	81 (70-90)	79 (66-90)	78 (69-94)	83 (66-98)	76 (65-83)	0.093
	Normal ECG n(%) n=40	**ST elevation n(%) n=353**	**STD/TWI n(%) n=160**	**Global ischemia n(%) n=97**	**Q wave n(%) n=272**	**LBBB n(%) n=71**	**RBBB n(%) n=43**	**LVH n(%) n=82**	**Other ECG change n(%) n=66**	**p value**
Female	14 (35.0)	128 (36.3)	83 (51.9)	55 (56.7)	91 (33.5)	37 (52.1)	15 (34.9)	43 (52.4)	41 (37.6)	<0.001
Smoking	8 (21.6)	83 (24.9)	30 (20.0)	10 (11.9)	55 (22.3)	3 (5.1)	3 (7.7)	9 (12.2)	3 (5.6)	<0.001
Hypertension	18 (45.0)	177 (50.3)	88 (55.7)	60 (62.5)	136 (50.7)	42 (59.2)	19 (45.2)	51 (62.2)	41 (62.1)	0.100
Diabetes										0.040
Type 1	0 (0)	2 (0.6)	1 (0.6)	3 (3.1)	3 (1.1)	0 (0)	1 (2.3)	0 (0)	2 (3.0)	
Type 2	6 (15.0)	77 (21.8)	35 (22.0)	29 (30.2)	67 (24.7)	22 (31.4)	15 (34.9)	15 (18.3)	23 (34.8)	
Prior AMI	4 (10.0)	53 (15.2)	28 (17.9)	30 (30.9)	93 (34.8)	19 (27.1)	13 (30.2)	21 (25.6)	25 (38.5)	<0.001
PCI	6 (15.0)	87 (24.6)	17 (10.6)	10 (10.3)	33 (12.1)	3 (4.2)	3 (7.0)	4 (4.9)	9 (13.6)	<0.001
CABG	4 (10.0)	26 (7.4)	10 (6.3)	27 (27.8)	27 (9.9)	5 (7.0)	4 (9.3)	6 (7.3)	2 (3.0)	<0.001
TnI positive	18 (45.0)	324 (91.8)	113 (70.6)	96 (99.0)	234 (86.0)	60 (84.5)	34 (79.1)	68 (82.9)	47 (71.2)	<0.001

Medication at admission										
β blocker	16 (41.0)	142 (40.3)	87 (54.4)	65 (67.0)	135 (49.6)	35 (49.3)	22 (51.2)	45 (54.9)	38 (57.6)	<0.001
Diuretic	6 (15.4)	70 (19.9)	49 (30.6)	49 (50.5)	94 (34.6)	42 (59.2)	16 (37.2)	37 (45.1)	36 (54.5)	<0.001
Statin	9 (23.1)	65 (18.4)	47 (29.4)	26 (26.8)	55 (20.2)	14 (19.7)	8 (18.6)	17 (20.7)	20 (30.3)	0.121
ACE inhibitor	2 (5.1)	54 (15.3)	26 (16.3)	27 (27.8)	69 (25.4)	23 (32.9)	12 (27.9)	19 (23.2)	24 (36.4)	<0.001
ARB	4 (10.3)	19 (5.4)	13 (8.1)	5 (5.2)	21 (7.7)	6 (8.5)	1 (2.3)	11 (13.4)	3 (4.5)	0.232
ASA	19 (48.7)	124 (35.1)	72 (45.3)	54 (56.3)	124 (45.6)	32 (45.7)	20 (46.5)	41 (50.0)	41 (62.1)	0.001
Clopidogrel	1 (2.6)	4 (1.1)	2 (1.3)	1 (1.0)	2 (0.7)	1 (1.4)	1 (2.3)	0 (0)	0 (0)	0.888
Nitrate	19 (48.7)	118 (33.4)	75 (46.9)	69 (71.1)	128 (47.1)	48 (67.6)	24 (55.8)	44 (54.3)	39 (59.1)	<0.001
CCB	10 (25.6)	71 (20.2)	35 (21.9)	27 (27.8)	45 (16.5)	16 (22.5)	12 (27.9)	16 (19.5)	16 (24.2)	0.379
Digoxin	1 (2.6)	19 (5.4)	15 (9.4)	18 (18.6)	29 (10.7)	19 (26.8)	8 (18.6)	25 (30.5)	9 (13.6)	<0.001
Warfarin	1 (2.6)	21 (5.9)	17 (10.6)	15 (15.5)	38 (14.0)	17 (23.9)	5 (11.6)	12 (14.6)	17 (25.8)	<0.001
Medication at discharge										
β blocker	34 (85.0)	333 (94.3)	148 (92.5)	93 (95.9)	256 (94.1)	64 (90.1)	39 (90.7)	77 (93.9)	56 (84.8)	0.067
Diuretic	13 (32.5)	157 (44.5)	80 (50.0)	87 (89.7)	187 (68.8)	59 (83.1)	28 (65.1)	63 (76.8)	45 (68.2)	<0.001
Statin	25 (62.5)	256 (72.5)	86 (53.8)	58 (59.8)	146 (53.7)	25 (35.2)	15 (34.9)	36 (43.9)	29 (43.9)	<0.001
ACE inhibitor	4 (10.0)	167 (47.3)	56 (35.0)	38 (39.2)	159 (58.5)	43 (60.6)	18 (41.9)	37 (45.1)	29 (43.9)	<0.001
ARB	4 (10.0)	21 (5.9)	16 (10.0)	6 (6.2)	22 (8.1)	5 (7.0)	1 (2.3)	10 (12.2)	4 (6.1)	0.446
ASA	35 (87.5)	332 (94.1)	141 (88.1)	80 (82.5)	241 (88.6)	55 (77.5)	34 (79.1)	71 (86.6)	51 (77.3)	<0.001
Clopidogrel	9 (22.5)	115 (32.6)	29 (18.1)	16 (16.5)	43 (15.8)	6 (8.5)	5 (11.6)	9 (11.0)	7 (10.6)	<0.001
Nitrate	22 (55.0)	252 (71.4)	103 (64.4)	81 (83.5)	204 (75.0)	52 (73.2)	35 (81.4)	65 (79.3)	44 (66.7)	0.003
CCB	14 (35.0)	54 (15.3)	32 (20.0)	25 (25.8)	35 (12.9)	14 (19.7)	10 (23.3)	22 (26.8)	12 (18.2)	0.003
Digoxin	2 (5.0)	27 (7.6)	17 (10.6)	30 (30.9)	49 (18.0)	19 (26.8)	6 (14.0)	26 (31.7)	16 (24.2)	<0.001
Warfarin	4 (10.0)	58 (16.4)	33 (20.6)	22 (22.7)	90 (33.1)	28 (39.4)	7 (16.3)	25 (30.5)	21 (31.8)	<0.001

STD=ST depression; TWI=T-wave inversion; AMI=acute myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass grafting; TnI=troponin I; ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; CRP=C-Reactive Protein; BP=blood pressure

5.2 Short- and Mid-term Outcomes in STEMI According to ECG Findings

5.2.1 Outcome and the Grades of Ischemia

Outcomes according to the grades of ischemia in Study I are shown in Table 5. Patients with G2I had the lowest 30-day mortality. Of the G2I patients, 6.8% died during the 30-day follow-up, whereas mortality in G3I was 14.8% and in the NG group 15.6%, p=0.003. The proportions were similar regarding 30-day cardiovascular mortality and in-hospital mortality. There was no difference in the incidence of 30-day re-infarction, stroke, or new unplanned CABG or PCI. One-year mortality was 25.2% in the NG group, 18.6% in G3I, and 10.3% in G2I, p<0.001. The Kaplan-Meier curves and Log-Rank test showed the lowest one-year survival rate in the NG group and the highest in G2I (p<0.001) (Figure 5).

In the logistic regression analysis (Table 6.), G3I was associated with a twofold risk of death at one year as compared to G2I (odds ratio 2.00, 95% CI 1.07-3.72). In the NG group, the risk was even higher (OR 2.95, 95% CI 1.79-4.84). Other high-risk features in the logistic regression univariate analysis were female gender, higher age, nonsmoking, diabetes, hyperlipidemia, hypertension, prior angina, prior congestive heart failure, prior TIA/stroke, renal insufficiency, acute heart failure denoted by Killip class >1, pathological Q waves, not receiving immediate reperfusion, and some of the medications.

In the multivariable analysis, G3I had an OR 2.36 for one-year mortality but the 95% CI was 0.924-6.03 and p=0.073, making the result statistically nonsignificant. However, the NG category showed a higher risk of death compared with G2I in the multivariable analysis (OR 2.82, 95% CI 1.36-5.85, p=0.005). Other high-risk features in the multivariable model were higher age and acute heart failure.

Maximum cTn levels were 3.93 μg/l (IQR 1.02-8.22) in G3I, 2.72 (1.00-5.38) in NG and 1.87 μg/l (0.463-5.15) in G2I, p=0.001.

Table 5. Outcomes according to the grades of ischemia.

	NG[1]	n=131	G2I[2]	n=458	G3I[3]	n=86	
	%	n	%	n	%	n	p value
In-hospital mortality	16.0	21	5.2	24	11.6	10	<0.001
30-day mortality	15.6	19	6.8	30	14.8	12	0.003
30-day CV mortality	14.8	18	6.4	28	12.3	10	0.007
30-day AMI	6.6	8	4.6	20	6.2	5	0.610
30-day stroke	0.8	1	1.6	7	3.7	3	0.284
30-day new non-elective CABG/PCI	2.5	3	3.0	13	2.5	2	0.939
One-year mortality	25.2	33	10.3	47	18.6	16	<0.001

CV = cardiovascular, AMI = acute myocardial infarction, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention

[1] in the NG group, 9 patients were lost for 30-day follow-up.

[2] in the G2I group, 19 patients were lost for 30-day follow-up.

[3] in the G3I group, 5 patients were lost for 30-day follow-up.

Table 6. Risk of death at one year according to the grades of ischemia. Results of the univariate and multivariable analyses.

	Univariate analysis			Multivariable analysis		
	OR	95% CI	p value	OR	95% CI	p value
Grade of ischemia						
G2I	Ref.			Ref.		
G3I	2.00	1.07-3.72	0.029	2.36	0.924-6.03	0.073
No grade	2.95	1.79-4.84	<0.001	2.82	1.36-5.85	0.005
Male	0.450	0.291-0.697	<0.001	1.26	0.632-2.50	0.514
Age	1.09	1.07-1.11	<0.001	1.05	1.02-1.09	0.002
Current smoker	0.489	0.269-0.890	0.019	1.31	0.584-2.95	0.511
Diabetes	2.63	1.63-4.25	<0.001	1.82	0.854-3.88	0.121
Hyperlipidemia	0.595	0.379-0.935	0.024	0.579	0.286-1.17	0.129
Hypertension	1.94	1.22-3.08	0.005	1.50	0.620-3.62	0.369
Prior STEMI	1.24	0.639-2.40	0.527			
Prior angina	2.00	1.21-3.28	0.007	1.69	0.885-3.23	0.112
Prior CHF	5.64	2.91-10.9	<0.001	1.45	0.455-4.62	0.529
Prior TIA/stroke	3.15	1.69-5.87	<0.001	1.79	0.663-4.82	0.251
Renal insufficiency	8.91	3.79-21.0	<0.001	1.40	0.325-6.02	0.653
Prior PCI	1.41	0.635-3.15	0.397			
Prior CABG	1.39	0.514-3.77	0.516			
Killip class >1	9.71	5.89-16.0	<0.001	5.83	2.91-11.7	<0.001
Time from symptom onset to ECG	1.00	1.00-1.00	0.443			
Time from symptom onset to treatment	1.00	1.00-1.00	0.826			
Pathological Q-waves	1.82	1.14-2.90	0.013	1.65	0.812-3.34	0.167

STEMI in anterior location	1.27	0.825-1.96	0.278			
Reperfusion therapy						
NRT	Ref.			Ref.		
FT	0.341	0.195-0.599	<0.001	1.05	0.397-2.75	0.929
pPCI	0.294	0.158-0.546	<0.001	0.980	0.369-2.60	0.968
ASA	2.16	1.39-3.37	0.001	1.15	0.534-2.47	0.722
Clopidogrel	3.11	0.765-12.7	0.113			
Warfarin	2.23	1.01-4.91	0.048	0.881	0.226-3.44	0.855
β blocker	3.04	1.95-4.75	<0.001	1.36	0.645-2.87	0.419
Calcium channel blocker	2.47	1.50-4.06	<0.001	1.69	0.761-3.75	0.197
Statin	1.21	0.722-2.04	0.465			
ACEi/ARB	1.63	1.02-2.60	0.042	0.635	0.293-1.37	0.248

Abbreviations: see Table 2. Variables with p<0.1 were included in the multivariable analysis.

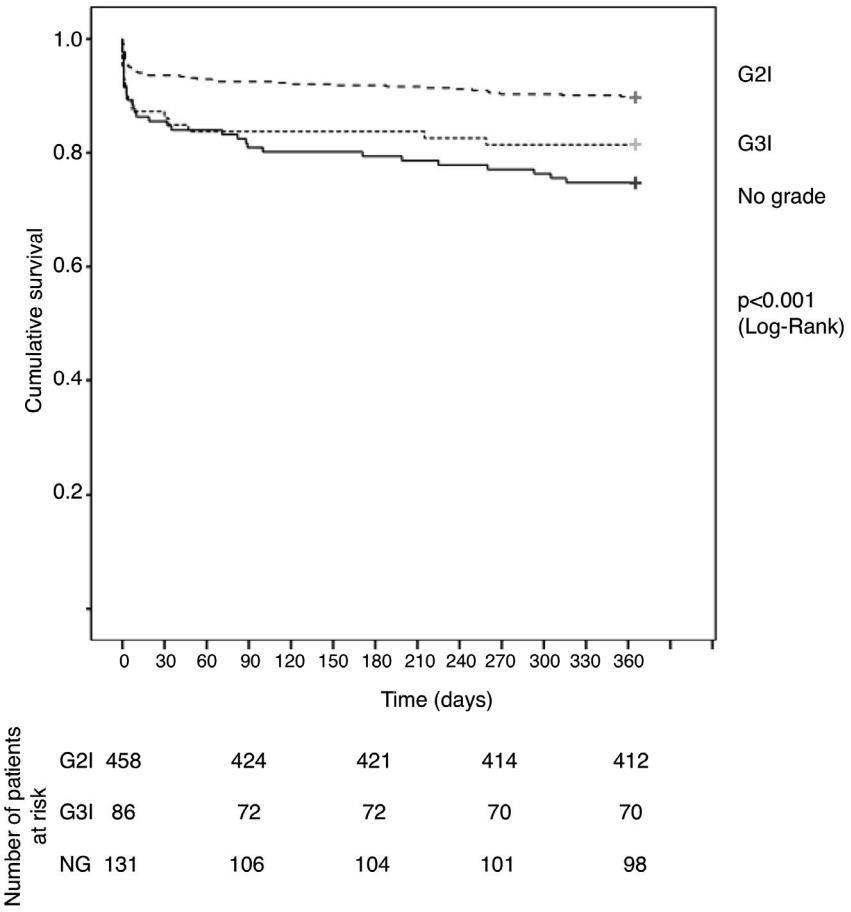

Figure 5. Kaplan-Meier analysis showing one-year survival according to the grades of ischemia.

5.2.2 Outcomes According to Q Waves and T-wave Inversion

In Study II, we found no statistically significant differences between the four groups at the endpoints of the 30-day follow-up. However, mortality differed between the groups at one year. The highest mortality was seen in the Q+TWI+ group (31.0%), followed by the Q-TWI+ (22.0%), Q+TWI- (19.2%), and Q-TWI- (9.8%) groups, p=0.002. The results are shown in Table 7.

The Kaplan-Meier survival analysis showed that survival differed between the four groups. The Q-TWI- group showed relatively good survival throughout the follow-up, and patients with the Q+TWI+ group had low survival early on. The p value for the difference of survival between the groups was <0.001 (Figure 6).

In the logistic regression univariate analysis, all other ECG groups showed significantly higher risk of death at one year as compared to patients with no Q waves or TWI. The highest risk was in the Q+TWI+ group (OR 4.14, 95% CI 1.77-9.68, p=0.001). The risk of death was nearly similar in the Q-TWI+ and Q+TWI- groups, OR 2.59 and 2.19, 95% CI 1.23-5.45 and 1.27-3.77, and p values 0.012 and 0.005 in the respective groups. Other patient characteristics related to higher risk of one-year mortality were female gender, higher age, nonsmoking, diabetes, no hyperlipidemia, hypertension, prior angina, congestive heart failure, prior TIA/stroke, renal insufficiency, acute heart failure (Killip class >1), not getting immediate reperfusion therapy, and certain medications (Table 8.).

In the multivariable model, Q+TWI+ predicted higher one-year mortality when compared to Q-TWI- (OR 7.14, 95% CI 2.05-24.9, p=0.002). The risk of death at one year in Q-TWI+ and in Q+TWI- did not differ from Q-TWI- in the multivariable model (OR 3.13, 95% CI 0.900-10.9, p=0.073, and OR 1.46, 95% CI 0.614-3.54, p=0.385, respectively). Other patient features associated with higher risk of death were higher age, no hyperlipidemia, and acute heart failure (Table 8.).

The highest maximum cTn levels were seen in the Q+TWI- group (3.23 μg/l, IQR 0.930-8.80), followed by the Q+TWI+ (2.81 μg/l, IQR 1.31-4.59), Q-TWI+ (2.59 μg/l, IQR 0.750-4.78), and Q-TWI- (1.81 μg/l, IQR 0.425-4.67) groups (p value for the difference between medians 0.002).

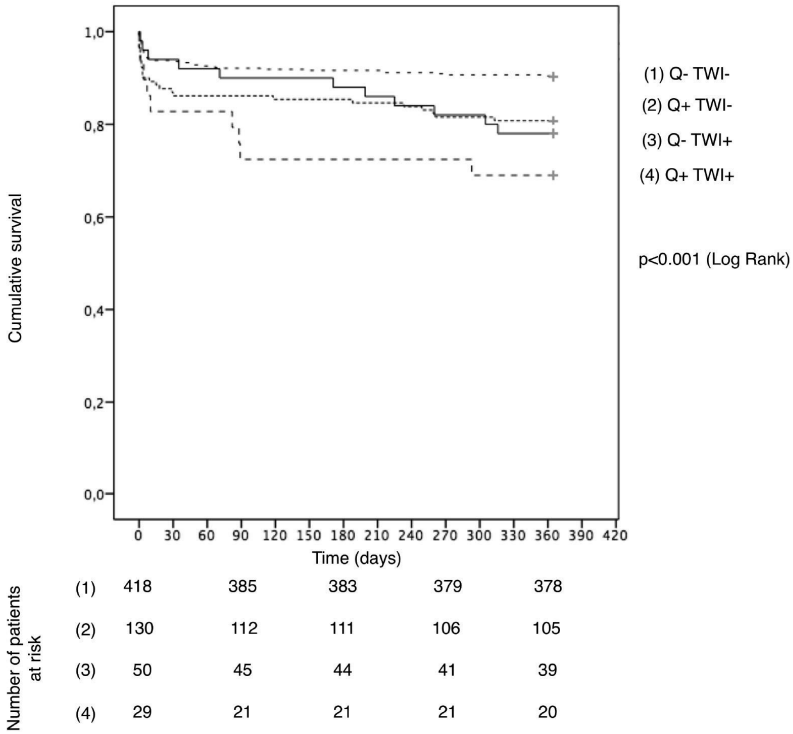

Figure 6. Kaplan-Meier analysis showing one-year survival according to the presence of Q waves and/or TWI.

Table 7. Outcomes according to the presence of Q waves and/or TWI.

	All n (%) n=627	Q+ TWI+ n (%) n=29	Q- TWI+ n (%) n=50	Q+ TWI- n (%) n=130	Q- TWI- n (%) n=418	p value
30-day follow-up						
30-day mortality	53 (8.9)	5 (20.0)	3 (6.4)	18 (14.4)	27 (6.8)	0.012
30-day CV mortality	47 (7.9)	4 (16.0)	3 (6.4)	14 (11.2)	26 (6.5)	0.126
30-day AMI	29 (4.9)	2 (8.0)	2 (4.3)	7 (5.6)	18 (4.5)	0.705
30-day stroke	11 (1.8)	0 (0)	0 (0)	4 (3.2)	7 (1.8)	0.655
30-day new non-elective CABG/PCI	15 (2.5)	0 (0)	0 (0)	2 (1.6)	13 (3.3)	0.578
Lost for follow-up	31	4	3	5	19	
In-hospital mortality	45 (7.2)	5 (17.2)	4 (8.0)	12 (9.2)	24 (5.7)	0.077
1-year mortality	86 (13.7)	9 (31.0)	11 (22.0)	25 (19.2)	41 (9.8)	<0.001

Abbreviations: see Table 5.

Table 8. Risk of death at one year according to the presence of Q waves and/or TWI.

	Univariate analysis			Multivariable analysis		
	OR	95% CI	p value	OR	95% CI	p value
ECG						
Q- TWI-	Ref.			Ref.		
Q+ TWI-	2.19	1.27-3.77	0.005	1.46	0.614-3.54	0.385
Q- TWI+	2.59	1.23-5.45	0.012	3.13	0.900-10.9	0.073
Q+ TWI+	4.14	1.77-9.68	0.001	7.14	2.05-24.9	0.002
Male	0.436	0.275-0.690	<0.001	1.72	0.782-3.765	0.179
Age	1.10	1.07-1.13	<0.001	1.06	1.02-1.10	0.001
Current smoker	0.495	0.265-0.924	0.027	1.07	0.442-2.59	0.881
Diabetes	2.65	1.59-4.40	<0.001	1.56	0.687-3.53	0.289
Hyperlipidemia	0.497	0.304-0.811	0.005	0.413	0.183-0.930	0.033
Hypertension	1.895	1.17-3.07	0.009	2.03	0.756-5.43	0.160
Prior STEMI	1.65	0.837-3.24	0.149			
Prior angina	1.94	1.14-3.29	0.014	1.24	0.603-2.54	0.561
Prior CHF	8.62	4.12-18.0	<0.001	1.43	0.402-5.07	0.582
Prior TIA/stroke	3.20	1.62-6.30	<0.001	1.66	0.549-5.00	0.370

Renal insufficiency	11.2	4.21-29.8	<0.001	1.79	0.316-10.1	0.512
Prior PCI	0.982	0.372-2.59	0.971			
Prior CABG	2.51	0.871-7.22	0.088	1.86	0.288-12.1	0.514
Killip class >1	10.8	6.39-18.3	<0.001	5.99	2.83-12.1	<0.001
Time from symptom onset to ECG	1.00	0.999-1.00	0.911			
Time from symptom onset to treatment	1.00	0.999-1.00	0.887			
STEMI in anterior location	1.41	0.894-2.22	0.14			
NRT	Ref.			Ref.		
FT	0.374	0.204-0.687	0.002	1.39	0.449-4.31	0.567
pPCI	0.353	0.182-0.684	0.002	1.25	0.397-3.92	0.705
Aspirin	2.35	1.47-3.76	<0.001	1.63	0.714-3.70	0.247
Clopidogrel	2.55	0.487-13.4	0.267			
Warfarin	2.31	0.998-5.35	0.050	1.24	0.284-5.44	0.772
β blocker	3.24	2.02-5.18	<0.001	1.57	0.704-3.48	0.272
Calcium channel blocker	2.17	1.27-3.70	0.005	1.23	0.504-3.01	0.648
Statin	1.02	0.577-1.81	0.938			
ACEi/ARB	1.64	1.00-2.70	0.050	0.521	0.218-1.24	0.141

Abbreviations: see Table 3. Variables with p<0.1 were included in the multivariable analysis.

5.3 ECG Findings and Long-term Mortality in ACS

In Study III, the Kaplan-Meier survival analysis showed differences in 10-year survival between the different ECG groups (Figure 7). Normal ECG was associated with favorable outcomes. The groups with the next best survival rates were ST elevation and ST depression/TWI with lower survival than normal ECG but better than of the rest of the ECG categories. Patients with LBBB had poor survival early on and the outcome remained worst among the groups throughout the follow-up. The other five groups (RBBB, Q wave, other ECG change, GI, and LVH) had survival rates between the ST depression/TWI and LBBB categories in this order ($p<0.001$ for the difference between the groups).

We adjusted the survival of each group with age and gender in the Cox regression analysis (Table 9). Survival of ST elevation, ST depression/TWI, and RBBB did not differ from the normal ECG category. LBBB showed the highest adjusted risk of death at the 10-year follow-up (hazard ratio 3.25, 95% CI 1.65-6.40, p=0.001). Outcomes were close to those of the category of other ECG changes (HR 3.01, 95% CI 1.56-6.09, p=0.001). Survival in LVH, Q wave, and GI was nearly similar and poor in each group (HR 2.53, 2.28, and 2.22; 95% CI 1.29-4.97, 1.20-4.32, and 1.14-4.31; p value 0.007, 0.012, and 0.019 in the respective groups). Higher age was associated with poor survival, but gender was not.

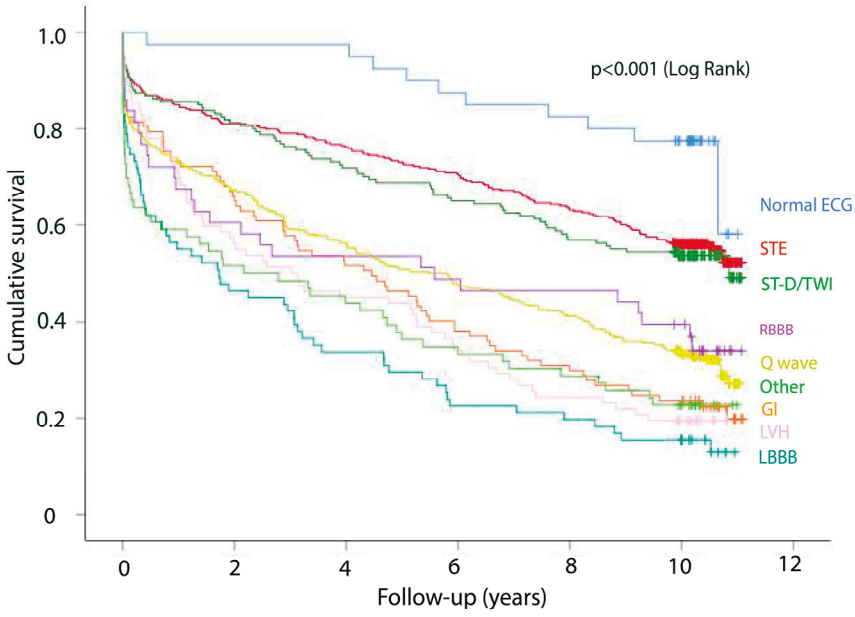

Figure 7. Kaplan-Meier survival analysis according to the ECG categories.

Table 9. Age- and gender-adjusted hazard ratios for 10-year mortality according to different ECG categories in ACS.

	HR	95% CI	p value
Normal ECG	Ref.	Ref.	Ref.
ST-D/TWI	1.45	0.74-2.81	0.277
STE	1.49	0.78-2.83	0.225
RBBB	1.84	0.89-3.82	0.100
GI	2.22	1.14-4.31	0.019
Q	2.28	1.20-4.32	0.012
LVH	2.53	1.29-4.97	0.007
Other ECG changes	3.01	1.56-6.09	0.001
LBBB	3.25	1.65-6.40	0.001
Age	1.07	1.06-1.08	<0.001
Gender (female)	0.90	0.77-1.06	0.199

ST-D=ST depression; TWI=T-wave inversion; STE=ST elevation; Q=Q wave; GI=global ischemia; LVH=left ventricular hypertrophy; LBBB=left bundle branch block

6 DISCUSSION

6.1 On Trials and Real-life Studies

The studies included in this thesis were essentially real-life ECG studies of patients with STEMI or other ACSs. ECG in ACSs has been extensively studied previously. However, most of the ECG studies included study subjects from clinical trials, which exclude a great number of patients. This is well illustrated in Table 1, which shows the numbers of excluded patients in the studies dealing with the grades of ischemia. Due to the great number of excluded patients, the studies may provide information that is not applicable to the handling of the everyday ACS patient population.

Of course, the non-randomized setting of a real-life study has challenges, too. In all three studies, it was evident that patients received different treatments in the different ECG groups. For example, in Study I, one-fourth of the patients in the No grade group received no immediate reperfusion therapy – more than double the corresponding rate of the two other groups. The one-year mortality of the No grade category patients was highest of the three studied groups. One may speculate whether the poor outcome in the No grade category solely expresses the high risk associated with this ECG feature or whether the outcome to a large extent was a result of deficiencies in treatment (Table 2 and Table 5).

It is also evident that patients in the different ECG groups have different baseline characteristics, which evidently could affect outcomes. One can easily see that in Studies I and II, the high-risk groups (No grade and Q+TWI+) had at least a trend toward a higher rate of comorbidities and medications than the other groups. In Study III, factors potentially associated with higher risk were distributed unevenly among the ECG groups. Should we then conclude that ECG is an inefficient tool for risk stratification in ACS, considering that the ECG categories could mainly reflect non-ECG risk factors and patients in the different ECG categories are treated differently? The answer is definitely no for at least two reasons.

Firstly, in risk stratification, one tends to mainly concentrate on outcomes. Based on our study results, we now know that STEMI patients with Q+TWI+ have worse outcomes than those without these features in their ECG. This is true even if the

poor outcome is a result of a cumulation of non-ECG risk factors in that group. This can also be looked at the other way around: by one glance at the ECG one can see that a patient probably has many risk factors for a poor outcome. This may also be valuable information when treating a patient – not merely the ECG.

Secondly, we can alleviate the influence of non-ECG risk factors and unevenly given treatments by performing logistic regression multivariable analysis. This was done in Studies I and II. In Study I, we saw that G3I doubled the risk of death as compared to G2I. However, the statistical significance was lost when adjusted with other risk factors. Two conclusions can be drawn: 1) G3I is definitely a high-risk feature in STEMI, and 2) the high risk of G3I may be associated with other high-risk features, such as acute decompensated heart failure.

Adjusting the outcome with other risk factors may have a downside as well. As stated above, G3I may be associated with acute heart failure. Thus, G3I is not an independent marker of poor outcome, as the poor outcome is explained by the higher incidence of acute heart failure in this group. G3I still remains a high-risk feature even if it is associated with both mortality and heart failure.

In Study III, we chose a slightly different approach to this problem of heterogeneous groups in a real-life study. We accepted that the groups are different and did not try to alleviate the influence of the different baseline characteristics. Our view was that ECG changes are "windows" onto all risk factors of a patient instead of being an independent risk factor. For example, poor outcome of LVH may be explained by a high incidence of hypertension in that group. LVH cannot be separated from hypertension because hypertension is the most common reason for LVH. This fact does not make LVH any worse a tool for assessing risk of death in ACS. Consequently, we chose to adjust the outcome with only age and gender in Study III.

6.2 On Follow-up Time and Definitions

Most of the representative studies on ECG in ACS have a follow-up of up to one year (Leivo et al., 2021; Siha et al., 2012). Studies with longer follow-ups are scarce (Hyde et al., 1999; Lahti et al., 2022; Mueller et al., 2004).

Long follow-up poses a problem. Treatments evolve at a rapid pace in cardiology. Current guidelines recommend pPCI for all eligible patients with STEMI (Ibanez et

al., 2018). In Study III, only 24.6% of the patients with ST elevation received PCI. We must therefore be cautious in interpreting the results. It is possible that the outcome of present-day STEMI patients is better than the outcome of the patients studied in Study III. Modern treatment has been reported to improve outcome in STEMI (Nauta et al., 2011). For example, in a recent all-comer registry study, Swedish STEMI patients had a 30-day mortality rate of 9.9% and a one-year mortality rate of 14.8% (Blondal et al., 2022). In an all-comer registry study from Finland, the mortality rate of STEMI patients was 22.5% during a median follow-up time of 3.7 years (Lahti et al., 2022). However, high-risk groups are likely to remain as such even when the treatments get better.

Patients with ACS are usually middle-aged or older. In Study III, the median age was as high as 77 years in some of the ECG groups (global ischemia, LBBB, RBBB, and LVH). It is clear that patients of this age have high long-term mortality rates irrespective of the ECG findings. This can, at least to some extent, be taken into account by adjusting the result with age and by choosing a suitable method for the analysis (Cox regression instead of binary logistic regression).

Definitions of ACS categories and ECG features also change over time. The TACOS study was the oldest of the three datasets used in this study. At the time of the TACOS study, the definition of ST elevation (described in section 4.2.1) was slightly different from the current definition in the Universal Definition (Thygesen et al., 2018). The differences are small: mainly there was a cut-off of 1.5 mm ST elevation of the precordial leads in our study, while the most recent version of the Universal Definition uses different cut-offs for men and women and for different age groups in leads V2-V3 and 1 mm in the other leads. It is very likely that all patients included in the STE group would fulfill the current criteria for STEMI, while some STEMI patients (according to the prevailing criteria) could have been excluded. However, there were only three patients with ST elevation/ST depression not fulfilling the criteria in the study population.

The definition of ST elevation in the HUS-STEMI and STEMI 2005 studies (section 4.1.1) were closer to the current definition than the definition used in the TACOS study. The main difference was that 2 mm ST elevation was required in V1 (1 mm in the Universal Definition), and 2 mm ST elevation was required in V2-V3 irrespective of age and gender (1.5 mm in females, 2.0 mm in males ≥40 y, and 2.5 mm in males <40 years in the Universal Definition). The two studies included STEMI patients, and presumably new LBBB was considered a STEMI equivalent.

Current guidelines recommend treating LBBB like NSTEMI i.e., performing pPCI only when suspecting ongoing ischemia (Collet et al., 2020).

Our definition of LBBB (section 4.2.7) is basically similar to the current definition by the ESC (Glikson et al., 2021). As reviewed in section 2.4.6, the current definition of LBBB has been challenged. It is possible that the stricter criteria proposed by Strauss et al. will increasingly be used in future studies on LBBB. (Strauss et al., 2011).

6.3 ECG in STEMI

6.3.1 Grades of Ischemia

G3I is a well-documented high-risk feature in STEMI (G. D. Birnbaum, Birnbaum, & Birnbaum, 2014). The proportion of G3I patients in the present study was 15.8% of the patients eligible for ischemia grading and 12.7% of all STEMIs. In previous studies, the percentage of G3I was consistently higher. In their groundbreaking study, Birnbaum et al found G3I in 43% of the studied STEMI patients (Y. Birnbaum, Sclarovsky, Blum, et al., 1993). Only anterior STEMIs eligible for ischemia grading were included. In a pPCI study by McGehee et al., the proportion of G3I was 42.6% of the patients eligible for ischemia grading. The percentage has been lower in most studies, typically between 20% and 35% (Table 1). The proportion of G3I of all STEMI patients was 27.5% in the GUSTO IIb study (Y. Birnbaum, Goodman, et al., 2001). It thus seems that our real-life study showed a clearly lower proportion of STEMI patients with G3I than the previous studies. We do not have any definite explanation for this difference, but it could be due to the fact that clinical studies have definite inclusion and exclusion criteria, while our study had no non-ECG exclusion criteria. It could be that for some reason clinical trials exclude mostly patients with G2I. The proportion of G3I was 13.4% of all STEMI patients in a registry study with 1,363 STEMI patients treated with pPCI (Lahti et al., 2022). This is line with our results in showing a lower proportion of G3I in real life.

The patient characteristics of our real-life patients were somewhat different from those seen in clinical trials: the median age was 69.5 years in the NG patients, 65.5 years in the G2I patients, and 66.8 years in the G3I patients. The mean age in the DANAMI-2 study was 63.5 years in G3I patients and 61.9 years in G2I patients (Sejersten et al., 2006). In the GUSTO IIb angiographic substudy, the mean age of

patients with G2I and G3I was 60 and 64 years, respectively (Y. Birnbaum, Goodman, et al., 2001). The ON-TIME 2 investigators reported a mean age of 60.9 years in G2I and 63.3 years in G3I (Postma et al., 2011). McGehee et al. had only ECG-related exclusion criteria in their study (McGehee et al., 2007). They found a mean age of 56 years in G2I and 60 years in G3I. However, only pPCI patients were included, which excluded STEMI patients not eligible for this treatment. The more recent TOTAL trial included pPCI patients, and the mean age was 60.3 years in G2I, and 61.5 years in G3I (Leivo et al., 2021). It seems that both G2I and G3I patients in clinical trials were consistently younger than the real-life patients included in the present study (Study I). Like in clinical trials in cardiology in general, older patients with comorbidities often tend to be excluded. Alternatively, they may not be eligible for the studied treatment. Indeed, many studies on the grades of ischemia were done in trials that excluded older patients (Y. Birnbaum et al., 2002; Postma et al., 2011)

6.3.1.1 Mortality and the Grades of Ischemia

In-hospital mortality was higher in Study I than in previous studies – 11.6% in G3I and 5.2% in G2I. Birnbaum, Herz et al. reported 6.8% in-hospital mortality in G3I and 3.8% in G2I (Y. Birnbaum, Herz, et al., 1996). Their study excluded patients not eligible for FT. The percentages were almost identical in another study comparing FT and pPCI, 6.8% in G3I and 3.2% in G2I (Y. Birnbaum, Goodman, et al., 2001). Some studies have reported no statistically significant difference in in-hospital mortality between G3I and G2I but the low number of patients is likely to affect these results (Garcia-Rubira, Garcia-Borbolla, et al., 2008; McGehee et al., 2007).

Our real-life study also showed higher 30-day mortality than previous studies: 30-day mortality was 14.6% in G3I and 6.8% in G2I. The studies reviewed in section 2.3.4.3.2 found 5.1%-9.7% 30-day mortality in G3I and 2.1-4.8% in G2I (Postma et al., 2011; Sejersten et al., 2006).

Some previous studies have reported one-year mortality rates of 5.2-18% in G3I (Y. Birnbaum, Kloner, et al., 1996; Leivo et al., 2021; Postma et al., 2011). These mortality rates are mostly lower than the 18.6% one-year mortality found in Study I. Birnbaum et al. found 18% mortality in G3I in FT-treated patients, which was nearly the same proportion as in Study I (Y. Birnbaum, Kloner, et al., 1996). Rommel et al. reported surprisingly low one-year mortality (3.3%) in G3I (Rommel et al., 2016). They enrolled 2,065 patients, of whom 572 had complete ECG and CMR data and were thus included in the study. It is likely that the exceptionally low reported

mortality in G3I is explained at least in part by the highly selected population in that study. The one-year mortality was nearly sixfold in our real-life population.

The mortality of the real-life study by Yilmaz et al. was close to the mortality found in Study I. They found 17.2% one-year mortality in G3I and 4.8% in G2I. The respective proportions were 18.6% and 10.3% in Study I. It is worth noting that in a recent registry study in pPCI patients, G3I did not predict higher mortality than G2I (Lahti et al., 2022). The explanation remains unclear, as the G3I patients were not the main subject of that study.

Our study showed that in a real-life setting, patients with G3I have a significantly higher mortality rate than patients with G2I, both in the short-term and mid-term. This result is in line with the previous studies. It seems that in real life, mortality is consistently higher in both G2I and G3I than in studies with selected populations.

6.3.1.2 No Grade of Ischemia

The most interesting finding of our study was not about G3I or G2I. It is evident from previous studies that G3I is an ECG manifestation associated with poor outcomes, and there is robust clinical data to support the increased risk for a rapidly progressing and deleterious pathophysiological process (Y. Birnbaum, Criger, et al., 2001; Leivo et al., 2021; Ringborn et al., 2014). However, one has to be cautious in interpreting the prognostic significance of G3I in STEMI, as many high-risk STEMI populations were excluded from the studies (Table 1).

We found that the STEMI patients not eligible for ischemia grading, i.e., patients with broad QRS or TWI, have even higher mortality than G3I patients. Thus, previous studies on the grades of ischemia may have ignored the STEMI population with the highest risk of death. Most studies on the grades of ischemia did not report the outcome of the excluded patients. The DANAMI-2 study reported a higher 30-day mortality rate among patients excluded from the study (12%) compared with the G3I (9.7%) and G2I patients (4.8%) (Sejersten et al., 2006). In the present study, 30-day mortality of the NG patients was 15.6%. It must be kept in mind that the patients excluded from the DANAMI-2 study and the NG group of the present study are not precisely similar. Our NG group only comprised STEMI patients not eligible for ischemia grading, whereas the group of patients excluded from the DANAMI-2 study also had missing/incomplete ECGs or no diagnostic ST elevation.

Several clinical features may explain the poor outcomes of the NG patients. Pre-existent congestive heart failure, renal insufficiency, and prior CABG were more common among the NG patients than among the other patients. They were also older, although the result lacked statistical significance. The rate of immediate reperfusion therapy was lower in the NG patients than in the rest of the study population. The high prevalence of comorbidities may have rendered the patients in the NG group more vulnerable to the deleterious effects of acute myocardial ischemia and infarction, and perhaps made them more prone to side effects of the treatment. Their older age and many comorbidities may also have made the patients non-eligible for life-saving treatments. The delay from symptom onset to treatment was clearly longest in the NG group. NG may represent later stages of evolving MI. TWI in particular may be a sign of progressed MI and poor outcome (Shimada et al., 2013). In conclusion, NG may imply higher risk of death than G3I, but it may be difficult to improve the outcomes of these patients.

Both components of NG – broad QRS and TWI – have been studied previously. TWI in STEMI is discussed in section 6.3.2. In the HERO-2 trial, patients with LBBB had clearly higher mortality than patients with no BBB, but this was associated with a cumulation of risk factors in that group (Wong, Stewart, et al., 2006). RBBB at admission also led to higher mortality. A Swiss registry study showed an almost twofold in-hospital mortality rate in patients with LBBB and confirmed AMI compared to STEMI patients (Erne et al., 2017). The higher risk of death in LBBB was lost when adjusted for other risk factors. In the registry study by Lahti et al., RBBB, LBBB, and nonspecific IVCD predicted unadjusted long-term mortality in pPCI-treated STEMI patients, while G3I did not (Lahti et al., 2022). LBBB and IVCD also predicted higher mortality in the multivariable analysis.

It seems that broad QRS is a high-risk feature in AMI and STEMI (partially due to the cumulation of risk factors in patients with broad QRS), and this is in line with the poor outcomes of the NG group of the present study.

6.3.2 The Components of Evolving MI – Q Waves and TWI

Previous studies have shown that ECG signs of EMI (Q waves and/or TWI) predict poor outcomes in STEMI (Eskola et al., 2007). In Study II, we sought to explore Q waves and TWIs separately and together to find what role each of these findings play in EMI. This has not been studied previously.

In the DANAMI-2 trial, EMI in the presenting ECG led to higher mortality and less benefit from pPCI (Eskola et al., 2007). EMI showed a higher risk for the composite endpoint at 2.7-year follow-up as compared to patients with no Q waves or TWI when adjusted with other risk factors. The statistical method, follow-up time, and endpoint differed from our study, but some comparisons can be made. In our multivariable model, Q waves alone did not independently predict mortality at one year, but TWI alone and Q waves and TWI together did.

6.3.2.1 Q Waves

The significance of Q waves has been extensively studied in STEMI patients. In our study, diabetes was more common among patients with Q waves, but there was no statistically significant difference in other comorbidities. In a large study made in the thrombolytic era, mean age was similar in patients with and without Q waves (Wong, Gao, Raffel, et al., 2006). However, some comorbidities (such as hypertension) were more common in the Q-wave group, but diabetes was slightly less common. In a large pPCI study, patients with Q waves were older and had more comorbidities than patients without Q waves (Armstrong et al., 2009). In both the previous studies and our study, for some reason, Q waves seem to be more common in males (Armstrong et al., 2009; Siha et al., 2012; Wong, Gao, Raffel, et al., 2006).

Interestingly, Q-waves seem to be more prevalent in anterior STEMIs than in other MI locations: this was the case in both our study and the previous studies (Armstrong et al., 2009; Wong, Gao, Raffel, et al., 2006). It is plausible that Q waves appear more easily in the precordial leads. Another possible explanation is that the area-at-risk is larger in anterior STEMIs. Q waves are known to reflect larger area-at-risk and larger infarcts (Delewi et al., 2013). In our study, patients with Q waves also had the highest maximum cTn levels, indicating larger infarcts. Acute heart failure denoted by Killip class >1 was more common in patients with Q waves. This could be a result of larger infarcts. The rate of Q waves is also dependent on the definition of pathological Q waves. This is most evident in the inferior leads, where less strict criteria, using the Q/R ratio, could result in a higher sensitivity to detect MIs, but at the cost of lower specificity.

Our study showed that Q waves alone indicated higher mortality at one year compared to the absence of both Q waves and TWI (although this effect was lost when adjusted with other risk factors). Previous studies have shown that Q waves indicate higher risk of death in both FT-treated (Y. Birnbaum et al., 1997; Wong,

Gao, Raffel, et al., 2006) and pPCI-treated patients (Armstrong et al., 2009; Siha et al., 2012). Our study is in line with previous studies in confirming the high mortality of STEMI patients with baseline Q waves.

6.3.2.2 T-wave Inversion

Our results show that TWIs are clearly a marker of poor outcome in STEMI. In the literature, the role of TWIs as a sign of poor outcome is less straightforward than the role of Q waves. Some studies report culprit artery patency (Alsaab et al., 2014; Hira et al., 2014), whereas some studies underline non-patency (Wong et al., 1999) and poor outcome in TWI (Shimada et al., 2013). Some of this discrepancy may be explained by the study by Herz et al. (Herz et al., 1999). In their study, late-presenting STEMI patients with TWI had higher mortality whereas the TWI patients presenting early had a tendency toward favorable outcome. Their cut-off for late presenters was two hours from symptom onset.

It has been well-documented in the literature that successful reperfusion is often seen as TWI in the ECG, and that this situation indicates favorable outcome after both FT (Sgarbossa et al., 2000) and pPCI (M. J. Lee et al., 2017). On the other hand, persistent TWIs in STEMI are associated with CMR-proven myocardial damage (Reindl et al., 2017). It seems that both early reperfusion and EMI may show similar TWIs in the ECG, and we may not have the tools to discern these two phenomena in the ECG. TWI in an early-presenting STEMI patient is more likely due to reperfusion, whereas late presenters with persistent STE and TWI may have evolved to the irreversible infarct stage as implied by Herz et al. (Herz et al., 1999). We can assume that the TWI groups of our study mostly comprised patients from the later stages of the disease process, as the median time from symptom onset to ECG was over three hours in both groups. This would also explain the poor outcomes in these patients.

6.3.2.3 Q Waves and T-Wave Inversion

The highest mortality was seen in patients with both Q waves and TWIs. The prognostic impact of the combination of Q waves and TWIs in STEMI patients has not been studied thoroughly. Wong et al. studied 362 STEMI patients from the HERO trial and found a Q+TWI+ configuration in 59 patients (Wong et al., 1999),

and this ECG feature was associated with a (normal) TIMI 3 flow in only 20% of the patients compared to 50% of the other patients.

One could possibly simplify the significance of Q waves and TWIs in STEMI as follows: Q waves represent large infarcts, while (at least late-presenting) TWIs represent established infarcts with nonreversible injury. From that perspective, the combination of these two ECG features would represent large and progressed infarcts, which naturally leads to poor outcome.

6.4 ECG in NSTE-ACS

6.4.1 STE vs. NSTE-ACS

Most of the studied ECG categories in the NSTE-ACS population had clearly worse outcomes than ST elevation at ten-year follow-up. In the Kaplan-Meier analysis, ST elevation indicated the second-best survival after a normal ECG at ten-year follow-up. The survival curve of ST elevation was very close to that of ST depression/TWI. When adjusted with age and gender, ST elevation did not differ significantly from normal ECG.

Previous studies have shown that STEMI patients do not necessarily have worse outcomes than NSTEMI patients in the long run. In a New Zealand-based study with a 12.7-year follow-up, mortality in NSTEMI was 61% compared with 58% for STEMI. Mortality was lowest in UA, 42%. A Korean study showed that mortality in STEMI was higher than in NSTEMI during the first 30 days but lower after 30 days at one-year follow-up (Park et al., 2013). In a French real-life study, in-hospital mortality was very similar in NSTEMI and STEMI, but at one year, NSTEMI had a tendency toward higher mortality (G. Montalescot et al., 2007).

The concept of STEMI was not created to find MI patients with high mortality. Instead, patients with ST elevation or BBB were found to benefit from thrombolysis (FTT, 1994), and thus ST elevation became the hallmark of impending cardiac necrosis. Our results imply that ST elevation is indeed not the ECG finding with the worst outcome in ACS. However, patients with ST elevation may be the ones whose outcome can be improved most by treatment (Nauta et al., 2011). The patients with ST elevation in our study underwent PCI more often (24.6%) than those in the other ECG categories, although the percentage is low at present-day standards. The higher

proportion of PCI in the STEMI group may indicate that these patients were treated more actively. This may have contributed to the relatively low mortality in this group.

One reason for the relatively favorable outcome of ST elevation in our study is the fact that 8.2% of the patients were cTn-negative. Some may have had transient ST elevation and others persistent non-ischemic ST elevation and unstable angina. The contemporary cTn assays were not as sensitive as the current highly sensitive assays. It is plausible that with modern methods, more troponin-negative patients would have been classified as cTn-positive.

6.4.2 ST Depression and T-Wave Inversion

The survival curve of ST depression/TWI was very close to that of ST elevation in the Kaplan-Meier analysis. ST depression/TWI did not differ significantly from normal ECG when adjusted with age and gender. Many previous studies have shown clearly poor outcomes in ST depression when compared to NSTE-ACS without ST depression, and even when compared to ST elevation (Hyde et al., 1999; Kaul et al., 2001; Savonitto et al., 1999). These studies have included global ischemia and perhaps ECG-LVH in the ST depression group. We studied these two features as separate groups and found them to be associated with worse outcomes than other ST depression/TWI. The poor outcome of ST depression as compared to ST elevation in the previous studies is at least partially explained by patients with global ischemia and ECG-LVH.

As reviewed in section 2.4.1, ST depression is not necessarily a sign of milder (subendocardial) ischemia than ST elevation, which was the former concept (Ekmekci et al., 1961). ST depression in the precordial leads may reflect acute coronary occlusion of any of the three main coronary arteries, most typically the LCx area (Meyers et al., 2021; Verouden et al., 2009; T. Y. Wang et al., 2009). Thus, many of the patients with ST depression in our study may have had acute coronary occlusion without ST elevation in their ECG. The survival of such patients is likely to be close to that of ST elevation.

We studied ST depression and TWI together as a single group. The prognostic role of TWI in NSTE-ACS is not clear. Tan et al. studied the importance of TWI in NSTE-ACS patients with or without ST depression (Tan et al., 2013). They found TWI to be a marker of high risk of death. This risk was associated with other risk features, and TWI had no independent prognostic significance. Patients with ST

depression had higher in-hospital and six-month mortality. The highest mortality was found in patients with both ST depression and TWI. The authors concluded that TWI has no incremental value in assessing the outcome of NSTE-ACS when compared to ST depression. This conclusion was drawn from the performance of TWI in the multivariable model. As discussed earlier, our aim was to study the total risk of a patient reflected by the ECG – not the independent role of a single ECG feature. Thus, we think that adding TWI to the risk analysis may be valuable.

Several studies have reported relatively favorable outcome in NSTE-ACS patients with TWI, but one has to be cautious when comparing the results with Study III. Sarak et al. found that persistent or resolving TWI did not predict mortality when adjusted with risk factors, although there was higher unadjusted mortality in these groups (Sarak et al., 2016). Savonitto et al. also reported favorable outcomes in TWI, but they used TWI as the reference group for ST depression and ST elevation. Patients with normal ECG were not included in the study (Savonitto et al., 1999). However, Patel et al. reported both lower unadjusted and adjusted in-hospital mortality compared to normal ECG in a very large registry study (Patel et al., 2014). In our real-life study, ST depression/TWI does not stand out as a group with more risk factors than the other groups (Table 4). We did not investigate the outcome of isolated TWI. According to the previous studies, it is likely that combining TWI with ST depression may have alleviated the higher mortality of the ST depression/TWI group in Study III.

Anterior TWI in NSTEMI may also reflect critical stenosis of the LAD leading to a disease that may evolve into an anterior MI (de Zwaan et al., 1982; Haines et al., 1983). These patients may have contributed to the STEMI-like outcome of our ST depression/TWI group.

Previous studies have reported both higher (although head-to-head comparison between the two groups was not done) (Hyde et al., 1999) and lower (Mueller et al., 2004) long-term mortality in TWI compared to normal ECG. Both studies report higher long-term mortality in ST depression. In our study, combining ST depression with TWI did not make the outcomes of this combined group necessarily poor. This is probably due to the exclusion of global ischemia and ECG-LVH from this group.

6.4.3 Global Ischemia

Global ischemia was clearly one of the highest-risk ECG changes in our study. Long-term outcomes of global ischemia have not been studied previously, and data on short-term outcomes is scarce as well. As mentioned above, global ischemia has probably contributed to the poor outcome of patients with ST depression in previous studies. When compared to patients with ST depression and positive T waves, patients with global ischemia had a higher in-hospital mortality rate in a study by Nikus et al. (K. C. Nikus et al., 2004). Interestingly, many of the patients with anterior ST depression and positive T waves may have represented lateral STEMI equivalent (LCx occlusion) or the anterior de Winter phenomenon which is also considered a STEMI equivalent. Taglieri et al. compared one-year cardiovascular mortality of global ischemia patients to those with TWI, isolated ST depression, or ECG confounders (Taglieri et al., 2011), and global ischemia clearly had the highest CV mortality rate. Our results are in line with these studies, as the patients with ST depression/TWI clearly had better outcomes than those with global ischemia.

The poor outcome of global ischemia is probably explained by the complex coronary artery disease that this ECG finding reflects. We did not study the angiographic findings of our global ischemia patients, but this was studied previously. Global ischemia in the ECG is known to clearly raise the odds for LM or three-vessel disease (K. C. Nikus et al., 2004; Taglieri et al., 2011). The Universal Definition of MI states that ST depression ≥1mm in six leads or more and ST elevation in aVR and/or V1 indicates multivessel disease or LM disease (Thygesen et al., 2018). It is plausible that complex and severe coronary atherosclerosis leads to worse outcomes. Many risk factors, such as hypertension, type 2 diabetes, and prior MI, were more common in the global ischemia patients than in most ECG groups. This may also to some extent explain the poor outcome of global ischemia.

6.4.4 Q Waves

There are surprisingly few studies on the outcome of baseline Q waves in NSTE-ACS. We found that baseline Q waves clearly and significantly predicted higher mortality at 10-year follow-up compared with normal ECG.

According to Hersi et al., NSTE-ACS patients with Q waves on the discharge ECG had higher six-month mortality than those without Q waves (Hersi et al., 2003). They did not find statistically significant differences in the baseline Q waves and six-

month mortality. Alkaabi et al. studied baseline and follow-up Q waves in NSTE-ACS patients in a similar manner (Alkaabi et al., 2008). Like Hersi et al., they found no association between baseline Q waves (transient or not) and one-year mortality. We did not study follow-up ECGs and thus we do not know the proportion of patients with transient Q waves. According to our results, baseline Q waves indicate high long-term mortality. One must be cautious when comparing our results with those from previous studies. When using the dichotomy – Q waves vs. no Q waves – the reference group may include many high-risk ECG features, such as global ischemia, unlike in our study. There are no studies using precisely the same categorization of ECG changes as was the case in our study.

Q waves were traditionally thought to be a hallmark of myocardial necrosis (Savage, Wagner, Ideker, Podolsky, & Hackel, 1977) but later studies – like those mentioned above (Alkaabi et al., 2008; Hersi et al., 2003) – have revealed that baseline Q waves may be transient. Prior MI was common among patients with Q waves (34.8%) in our study population. Only patients with "other ECG change" had previous AMI more often (38.5%). The high number of previous MI in Q wave patients implies that the Q wave represented myocardial scarring at least in a substantial proportion of the patients. A second hit in an already scarred myocardium is likely to cause high mortality.

6.4.5 LBBB

LBBB stands out as the ECG change with the highest 10-year mortality in both the Kaplan-Meier analysis and the age-and-gender-adjusted Cox regression analysis in our study. The outcome of LBBB is known to be poor in STEMI studies as discussed above. It can also be questioned whether LBBB should be classified as STEMI or NSTE-ACS. A fairly recent study found that the culprit artery could be determined in 54.2% of patients with new LBBB (and 83.3% in patients with no new LBBB) in a population with suspected STEMI (Pera et al., 2018). We did not separate patients fulfilling the Smith criteria or other signs of ACO, and the LBBB group in Study III is likely to comprise both patients with and without ACO.

As reviewed in section 2.4.6, LBBB is associated with poor outcomes in studies on NSTE-ACS (Hyde et al., 1999), STEMI (with presumably new LBBB included) (Al-Faleh et al., 2006), and unselected AMI (Al Rajoub et al., 2017). It seems that LBBB is the ECG change with the highest risk of death throughout all types of ACS.

Our study fortifies this idea by showing the poor long-term outcomes of these patients.

When assessing outcomes of LBBB in STEMI, one must keep in mind that many STEMI studies have included patients with new or presumably new LBBB (Lahti et al., 2022). Probably, many of these patients did not have an acutely occluded coronary artery. Given the high specificity of the specific criteria for acute coronary occlusion in LBBB (Di Marco et al., 2020), studies using these criteria could be more reliable in assessing the significance of LBBB in STEMI (Al-Faleh et al., 2006).

6.4.6 ECG-LVH

LVH was one of the ECG categories with significantly high mortality in our long-term follow-up. In the Kaplan-Meier analysis, the survival of patients with LVH was very close to that of LBBB and global ischemia patients, that are notorious for their poor outcome. It may be somewhat surprising that LVH had such poor prognosis.

Many patients with LVH have secondary repolarization changes – so-called "strain." This is typically seen as ST depression in leads V5-V6 and as ST elevation in leads V1-V2 (-V3). Patients with LVH and strain have probably contributed to the poor outcome of NSTE-ACS patients classified as ST depression. In a study by Savonitto et al., the highest mortality rate was found in patients with both ST depression and ST elevation (Savonitto et al., 1999). It is likely that this high-risk group included patients with LVH and strain (with secondary ST elevation in the right precordial leads). Atar et al. found high mortality in NSTE-ACS patients with ST depression and TWI in leads V4-V6 (Atar et al., 2007). Also, in some of these patients, the ECG changes may have represented LVH and strain.

There are some studies focusing specifically on LVH in NSTE-ACS. Ali et al. found higher six-month mortality (not including in-hospital mortality) in LVH. When adjusted with other risk factors, LVH was not independently associated with in-hospital or six-month mortality (Ali et al., 2011). Again, the group with no LVH included other high-risk features such as global ischemia or Q waves, unlike in our study. One can also question the relevance of adjusting the multivariable analysis with many risk factors. For example, in the study by Ali et al., patients with LVH had a higher incidence of prior heart failure and hypertension, probably explaining part of the results. LVH was thus not an independent risk factor, but it still could be used to assess the total risk of death. LVH has also been shown to predict higher

long-term mortality in hypertensive patients without NSTE-ACS (Antikainen et al., 2006).

We also found that certain risk factors were common among patients with LVH (Table 4). LVH – with all the risk factors associated with it – was one of the strongest predictors of high mortality in NSTE-ACS.

6.4.7 RBBB

The significance of RBBB in NSTE-ACS has raised attention and been a matter of dispute since Widimsky et al. published their findings and claimed that RBBB in NSTE-ACS should be treated like STEMI due to the high risk of LAD occlusion (Widimsky et al., 2012). Still, only very few studies have explored the outcome of patients with RBBB and NSTE-ACS.

Our study placed long-term mortality of RBBB in the mid-part among the studied ECG categories in the Kaplan-Meier analysis. The survival curve was closest to that of Q waves. Survival was worse than in ST elevation and ST depression/TWI. The elevated risk of death lost its statistical significance when adjusted with age and gender. This may be partially due to the low number of patients (n=43) in that group.

Many studies have assessed the outcome of RBBB in STEMI or in unselected ACS populations (both STEMI and NSTE-ACS). An interesting study published in 2008 compared RBBB in STEMI and NSTEMI (Kleemann et al., 2008). RBBB was associated with higher one-year mortality in STEMI but not in NSTEMI.

Bansilal et al. had a seven-year follow-up in their study on patients with a first episode of angina (ST elevation excluded) resulting in an emergency department visit (Bansilal et al., 2011). In that study, patients with no BBB had better and those with LBBB worse survival than those with RBBB. These results resemble the results of our study in placing the mortality of RBBB halfway between LBBB and normal ECG.

In our study, many high-risk baseline features were common in the RBBB group. For example, type 2 diabetes was more common among RBBB patients (34.9%) than among those from the other groups (Table 4). In the aforementioned studies, RBBB also indicated a cumulation of risk factors when compared to the reference group (Bansilal et al., 2011; Kleemann et al., 2008). This may explain both the high mortality and the loss of significance in the multivariable model in RBBB.

6.5 Relevance of the Study Results in Clinical Practice

The big question is: can we use our results to guide the treatment of ACS patients. The answer is simple: no, we cannot. Our study only dealt with outcomes: more precisely with mortality in different ACS categories. ECG came into the spotlight in treating AMI after the Fibrinolytic Therapy Trialists´ Collaborative Group published their meta-analysis showing that patients with ST elevation or BBB benefited from FT more than other AMI patients (FTT, 1994). Since then, no ECG study has changed the paradigm of treating AMI. In a DANAMI-2 substudy, patients with the PIS or anterior Q waves with positive T waves benefited from pPCI over FT, while patients without these findings did not (Eskola et al., 2007). Also in a DANAMI-2 substudy, early-presenting G3I patients had a tendency toward better outcomes when treated with pPCI (Sejersten et al., 2006). Soon pPCI became the primarily recommended treatment in all cases of STEMI (Ibanez et al., 2018), and choosing between pPCI and FT by ECG became less relevant. Thrombus aspiration was the next promising opportunity for ECG to step onto the stage. It is known that, for example, G3I in the ECG implies a larger thrombus burden in angiography (Kurt et al., 2014). Unfortunately, a substudy from the large TOTAL trial showed no benefit from routine thrombus aspiration in G3I or other ECG groups (Leivo et al., 2021). PPCI is probably such an effective treatment modality that improving the results is challenging.

ECG could however be a window onto the patient's cardiac health and risk factors. It could thus provide a cheap and accessible tool for finding the right preventive treatment for the patient.

6.6 Future Perspectives

Our results show that among patients with STEMI (and thus very likely with acute coronary occlusion) mortality varies according to the ECG changes. Interestingly, long-term outcomes do not seem to be worst in the ACS patients with the highest likelihood of acute coronary occlusion i.e., patients with ST elevation. What then could be done to improve patient care in the categories with the highest risk of death? It seems that there is little room for improvement in opening occluded arteries. So far, the studied therapeutic strategies have not been successful. However, it would be useful if patient randomization in future studies with promising pharmacological

approaches could include ECG parameters. We are certainly available to point out high-risk ECG markers as potential candidates for randomization.

One important step would be to test the validity of the occlusive MI (OMI) concept in larger and prospective trials (Pendell Meyers et al., 2021). According to this classification (occlusive vs. non-occlusive myocardial infarction), some patients previously treated as NSTE-ACS should be treated with pPCI as in STEMI. The OMI classification includes many ECG findings, such as minor ST elevation with reciprocal ST depression, that already alert the clinician to consider emergent invasive evaluation in patients with symptoms likely caused by ischemia. So far, the studies have been retrospective and rather small. There are challenges with the OMI concept, such as the definition of cut-off values for significant "minor" ST elevation and ST depression.

Knowing the odds of survival is valuable information even when it does not affect the given treatment. When patients are diagnosed with a severe disease, their first question tends to be whether it will kill them prematurely. Roughly knowing the prognosis also helps doctors to orientate in treating a patient. Especially in high-risk patients, it is important to implement all effective treatment modalities. Our studies shed light onto the prognosis of STEMI patients and other ACS patients in real life.

6.7 Study Limitations

The present study has several limitations, which may affect the applicability of the results.

The ECGs were read by the researchers, and usually only one researcher read each ECG. In cases of doubt, consensus on the ECG analysis was sought with a group of researchers. The human eye is always prone to errors and biases. Using computer analysis could make the results more uniform. Another option could be to let several researchers read the ECGs and report possible differences in the analyses. Previous studies have shown that there is some interobserver variability in assessing ECG with the human eye (Billgren et al., 2004; Koivumaki et al., 2015).

The three datasets used in the present study required written informed consent from the patients. There is no information on patients who did not give their consent. This could theoretically lead to selection bias. There may have been patients who died soon after having the ECG taken or were unconscious, and these patients

were not able to give their consent. This may have led to excluding those patients at highest risk of death.

Echocardiographic findings were not available for the three studies. Thus, we had to assess heart failure indirectly i.e., by Killip class. Heart failure is an important prognostic factor in acute coronary syndromes, and information on the echocardiographic findings could have been useful.

The baseline information was gathered by the investigators-on-site and study nurses. Information was received from the patients and from the electronic patient records. Information gathered in this manner may not be complete.

Management of ACSs has changed vastly in the last few decades. The patients of the TACOS study were enrolled in 2002-2003. The STEMI 2005 study enrolled patients in 2005, and HUS-STEMI in 2007-2008. The contemporary treatment of STEMI and other ACSs differed in many ways from the present-day practice of treatment. It is plausible that the outcomes of ACS patients with present-day treatments are better than in our studies. This is, however, unlikely to affect the hierarchy of different ECG findings in assessing outcomes. For example, patients with Q+TWI+ remain at higher risk even with the improvements in treatment. This issue is discussed in section 6.2.

7 SUMMARY AND CONCLUSIONS

Although the ECG was introduced into clinics more than a century ago, it is still an effective tool for assessing the risk of adverse events and guiding treatment in all patients with suspected ACS. Previous studies have shown that ACSs can be categorized into several different groups according to their ECG features. These groups vary with respect to associated risk factors and outcomes. ECG provides an easy and readily available tool to assess patient prognosis and sometimes to choose the most suitable treatment.

We studied consecutive real-life patients with STEMI and other ACSs. We investigated the mortality of STEMI patients at one-year follow-up. The role of Q waves and TWIs was investigated. We studied the mortality of STEMI patients with G2I and G3I and with ECG changes excluding the patient from ischemia grading. Consecutive ACS patients were studied to find the weight of different ECG findings in predicting 10-year mortality.

The principal study findings were:

- G3I predicts higher mortality than G2I in real-life STEMI patients.
- Patients with No grade of ischemia in their ECG were at higher risk of death at one year than G3I or G2I. This result was independent of other risk factors.
- Q waves and TWI predicted higher mortality in STEMI than no Q waves or TWI.
- When assessing the prognostic impact of Q waves and TWI alone or in combination in STEMI, the highest one-year mortality was found in patients with both Q waves and TWI.
- Various pre-specified ECG categories reflected different patient profiles (baseline characteristics) in ACS.
- Patients with LBBB were at the highest risk of death during the 10-year follow-up.

- LBBB, other ECG changes, ECG-LVH, Q waves, and global ischemia predicted 10-year mortality irrespective of age and gender.

Conclusions: The present study confirmed the poor outcome of G3I in real life when compared to G2I. However, we found that patients excluded from ischemia grading are at an even higher risk of death. Q waves and TWI have long been used to assess outcome of STEMI patients. Our results revealed the prognostic role of these ECG changes when they occur alone or together. The 10-year follow-up of ACS patients shed light on the outcome of different ECG categories in ACS. There were substantial differences in mortality between the different ECG categories during the follow-up.

More than a century since its introduction into clinics, the ECG still remains an excellent tool for assessing the outcomes of patients with ACS.

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PUBLICATION I

Outcome of all-comers with STEMI based on the grade of ischemia in the presenting ECG.

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Outcome of all-comers with STEMI based on the grade of ischemia in the presenting ECG

Kimmo Koivula, MD [a,b,*], Markku Eskola, MD [b,c], Juho Viikilä, MD [d], Jyrki Lilleberg, MD [e], Heini Huhtala, MSc [f], Yochai Birnbaum, MD [g], Kjell Nikus, MD [b,c]

[a] Internal medicine, Helsinki University Hospital, Finland
[b] Faculty of Medicine and Life Sciences, University of Tampere, Finland
[c] Heart Center, Department of Cardiology, Tampere University Hospital, Finland
[d] Cardiology, Helsinki University Hospital, Finland
[e] Department of Internal Medicine, Hyvinkää Hospital, Hyvinkää, Finland
[f] Faculty of Social Sciences, University of Tampere, Finland
[g] The Section of Cardiology, The Department of Medicine, Baylor College of Medicine, Houston, TX, USA

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ABSTRACT

Background: Grade 3 ischemia (G3I) in the 12 lead electrocardiogram (ECG) predicts poor outcome in patients with ST-elevation myocardial infarction (STEMI). The outcome of G3I in "real-life" patient cohorts is unclear.
Methods: The aim of the study was to establish the prognostic significance of grade 2 ischemia (G2I), G3I and the STEMI patients excluded from ischemia grading (No grade of ischemia, NG) in a real-life patient population. We assessed in-hospital, 30-day and 1-year mortality as well as other endpoints.
Results: The NG patients had more comorbidities and longer treatment delays than the two other groups. Short-term and 1-year mortality were highest in patients with NG and lowest in patients with G2I. Maximum troponin level was highest in G3I, followed by NG and G2I. In logistic regression multivariable analysis, NG was independently associated with 1-year mortality.
Conclusions: NG predicted poor outcome in STEMI patients. G2I predicted relatively favorable outcome.

Introduction

In ST-elevation myocardial infarction (STEMI), the electrocardiogram (ECG) provides crucial diagnostic and prognostic information especially in the acute phase of the disease process. Grade 3 ischemia (G3I), as defined by the Sclarovsky-Birnbaum grading system [1,2], has been confirmed as a strong predictor of poor outcome and lower probability of ST-segment resolution in patients treated with either fibrinolytic therapy (FT) [3,4] or primary percutaneous coronary intervention (pPCI) [4,5]. Patients with G3I have larger infarcts [6,7], more microvascular damage [8] and a higher thrombus burden [9] than patients with Grade 2 ischemia (G2I). There is also more rapid progression of myocardial necrosis over time and less myocardial salvage in patients with G3I [10]. Evolution or persistence of G3I from the pre-hospital to the pre-PCI ECG predicts larger infarct size and less myocardial salvage compared to patients with persisting G2I or with decreasing grade from G3I to G2I [7]. Furthermore, G3I predicts reduced left ventricular regional wall motion [11], lower ejection fraction and more left ventricular remodeling in STEMI patients treated with PCI [12].

The differences in the underlying pathophysiological mechanisms of the different grades of ischemia (GI) have not been well established. The original hypothesis by Sclarovsky and Birnbaum, indicating differences in myocardial protection by subtotal occlusion, collateral flow or myocardial preconditioning, have been supported by previous studies, which showed a more rapid progression of myocardial necrosis in G3I [10].

Per definition, patients with T-wave inversions, ventricular rhythm, left or right bundle branch block or other ventricular conduction defects are excluded from the ischemia grading [2], but there is no study data on the outcome of these patients. Previously, it has been shown that a broad QRS in STEMI predicts adverse outcome [13]. T-wave inversions also predicted higher mortality in STEMI – at least in late-presenting patients [14].

Although many studies have established the importance of the grade of ischemia classification in the risk assessment of patients with STEMI,

Abbreviations: ECG, Electrocardiogram; GI, Grade of ischemia; G2I, Grade 2 ischemia; G3I, Grade 3 ischemia; NG, No grade of ischemia; STEMI, ST elevation myocardial infarction; FT, Fibrinolytic therapy; PCI, Percutaneous coronary intervention; pPCI, Primary percutaneous coronary intervention; NRT, No reperfusion therapy; MACE, Major adverse cardiovascular events; CABG, Coronary artery bypass grafting; CV, Cardiovascular; OR, Odds ratio; CI, Confidence interval; ACE, Angiotensin convertase.

* Corresponding author at: Helsinki University Hospital/Internal Medicine, Stenbäckinkatu 9, PL 100, 00029 HUS, Finland.
E-mail address: kimmo.koivula@helsinki.fi (K. Koivula).

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it remains unclear whether this is the case in "real-life" STEMI populations without specific exclusion criteria.

The aim of the present study was to evaluate the prognostic role of the GI in a STEMI population with only ECG-related exclusion criteria and to study the outcome of patients excluded from ischemia grading.

Material and methods

Study population

This study comprised two Finnish non-randomized STEMI studies. The STEMI 2005 study was conducted in the region of the Tampere University Hospital with a population of ≈1.2 M. Data on the incidence, demographics, treatment strategies and delays were collected for consecutive STEMI patients ($n = 310$) in four hospital districts during a six-month period [15]. Regarding reperfusion therapy, both pPCI and FT were used. The study was observational and treatment choices were based on prevailing international and regional guidelines.

In the HUS-STEMI study, patients ($n = 448$) were included during one year (2007–2008) in the district of the Helsinki University Hospital with a population of ≈1.6 M [16]. The choice of reperfusion therapy - FT or pPCI - was based on the decision by the consulting cardiologist. FT was recommended for hemodynamically stable patients when the time from symptom onset to treatment was ≤3 h. As in the STEMI 2005 study, use of ancillary anti-thrombotic therapy was based on prevailing guidelines and the study was observational.

The distribution of "No grade" (NG = patients excluded from ischemia grading based on ECG findings), G2I and G3I was 20%, 69% and 10% in the STEMI 2005 study, and 19%, 67% and 14%, respectively in the HUS-STEMI study (p value for the differences 0.319).

There were no pre-specified exclusion criteria in the two studies. The inclusion criteria were as follows:

Acute chest pain/discomfort and

1) ST-elevations of ≥0.2 mV in at least 2 of the leads V1–3 and/or,
2) ST-elevations of ≥0.1 mV in at least 2 other contiguous leads (V4–6; I, aVL; II, III, aVF) or,
3) New or presumably new left bundle branch block.

The local Ethics Committees approved the study protocol. A written informed consent was signed by the patients before enrollment.

Renal insufficiency was defined as creatinine >150 μmol/l (1.70 mg/dl) on admission. We used troponin T for the maximum troponin level with a cut-off <0.01 μg/l.

For the present study, mortality data were collected from the official national registry (Statistics Finland) and regarding in-hospital and 1-year mortality, no patients were lost for follow-up. Regarding other endpoints, data from the two studies were used. Data were not available for 33/679 (5%) patients at 30-day follow-up.

The patients were divided into three groups according to the revascularization strategy: FT with or without rescue-PCI, pPCI and "No reperfusion therapy" (NRT). The latter was defined as no FT or PCI within 4 h from presentation.

The primary endpoint was mortality at one year. Other pre-specified endpoints were in-hospital mortality, 30-day mortality and 30-day MACE (major adverse cardiovascular events, a composite of cardiovascular death, stroke, re-infarction and new, unplanned revascularization procedures).

ECG analysis

The ECG data were analyzed by one of the investigators (KK), who at the time of analysis was blinded to the clinical data. In borderline cases ($n = 100$), a consensus was sought together with 2–3 senior cardiologists (ME, KN and YB). Patients with missing/incomplete ($n = 25$), or non-interpretable ECG-recordings ($n = 12$) were excluded. Although included in the two studies by the investigators on-site, we found that the ST-elevations did not fulfill the inclusion criteria in 46/758 (6%) patients. These patients were excluded. A total of 675/758 (89%) patients were included in the final study group: 278/310 (90%) from the STEMI 2005 and 397/448 (89%) from the HUS-STEMI study. For ischemia grading, all other standard leads than aVR were used.

Pathological Q waves were defined according to the Third Universal Definition of Myocardial Infarction [17] and patients with pathological Q waves were included in the GI analysis. Pathological Q waves outside the leads with maximal ST elevation were ignored.

G3I was defined as distortion of the terminal portion of the QRS complex in at least two adjacent leads. In an rS type complex, typically in leads V1–V3, elevation of the S wave to or above the base line was defined as G3I (Fig. 1). In a qR type complex, typically in all the other leads, elevation of the J point ≥50% of the height of the R wave was considered as G3I (Fig. 2). In the presence of left axis deviation ($\leq -30°$) and S waves in V5–V6, disappearance of the S wave in V4 was interpreted as G3I [2]. The ECG was graded according to the most severe ischemia regardless of the infarct localization. For example, patients with anterior (anterolateral) STEMI were classified as G3I if they had G3I in the lateral leads I and aVL.

There were 131 patients in whom it was not possible to define the grade of ischemia. These patients formed the NG group in the present study (Fig. 3). The NG group consisted of patients with any T-wave inversion ≥0.05 mV in the leads with the maximum ST elevation and QRS duration ≤120 ms ($n = 79$) and patients with a QRS complex wider than 120 ms ($n = 52$), including 15 right bundle branch block, 13 left bundle branch block, 18 non-specific intraventricular conduction delay, 4 atrioventricular dissociation with ventricular rhythm, 1 accelerated idioventricular rhythm and 1 ventricular paced rhythm.

Statistical analysis

The data were analyzed with SPSS Statistics 22. We compared NG, G2I and G3I with respect to different pre-specified variables. In all categorical variables, we used the χ^2 test or Fisher's exact test. Because the distribution of all continuous variables was skewed, we used median values and used the Mann-Whitney U test or Kruskal-Wallis test for the difference between the groups. Interquartile ranges were defined using the weighted average.

We performed a logistic regression univariate analysis for the grades of ischemia using one-year mortality as the endpoint. We present odds ratios (OR) with 95% confidence intervals (CI). The variables with a p-value <0.1 were chosen for the multivariable analysis. In case of missing data, valid percentages are reported.

Results

G2I was found in 67.9% ($n = 458$), G3I in 12.7% ($n = 86$) and NG in 19.4% ($n = 131$) (Fig. 4). The baseline characteristics are shown in Table 1. Patients in the NG group more often had prior congestive heart failure than G2I or G3I (12.4%, 5.2% and 1.2%, respectively, $p = 0.001$) patients. The rate of prior CABG was 10.7%, 2.6% and 1.2% in the respective groups ($p < 0.001$). Killip class >1 was found in 46.6%, 26.1% and 32.9%, respectively ($p < 0.001$). The patients with NG were more often on angiotensin convertase inhibitor (ACE) inhibitor or angiotensin receptor blocker medication (34.6%) as compared to G21 (23.9%) and G3I (22.4%), patients ($p = 0.036$). The rate of pPCI in the NG, G2I and G3I groups was 42.7%, 33.6% and 29.1%, respectively ($p = 0.075$). Patients in the NG group were less often treated with FT (32.1%, 56.8% and 62.8%; $p < 0.001$) and had the highest rate of no acute reperfusion therapy (25.2%, 9.6% and 8.1%; $p < 0.001$).

The NG group had the longest median delay from symptom onset to ECG (172 min, quartiles 69–380) as compared to the G2I (80 min, quartiles 41–172) and G3I (75 min, quartiles 42–182) groups. p Value for the difference was <0.001. The median delay from symptom onset to

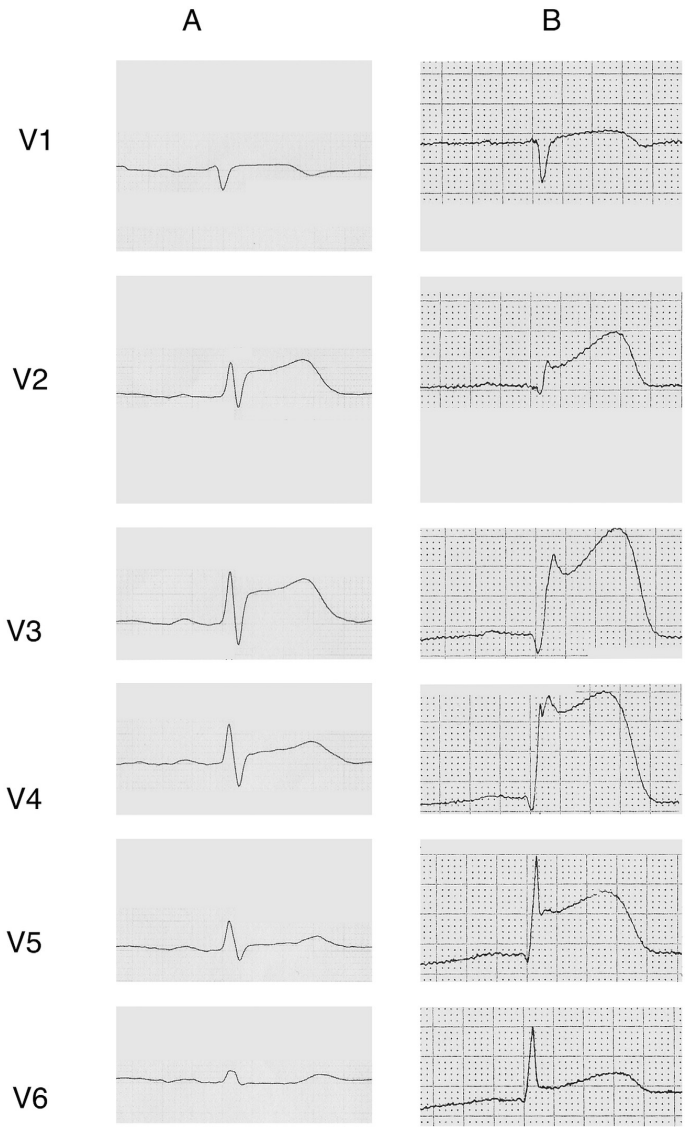

Fig. 1. Grade 2 ischemia (Panel A) and grade 3 ischemia (Panel B) in anterior STEMI (50 mm/s). In an rS type complex (typically V1–V3), G3I is shown as rising of S-wave above baseline.

treatment was 286 min (quartiles 144–556), 150 min (quartiles 91–248) and 110 min (quartiles 72–215), $p < 0.001$, respectively. We found no significant differences between the groups regarding rate of current smoking, diabetes, hyperlipidemia, hypertension, prior STEMI, prior angina pectoris, prior transient ischemic attack or stroke, renal insufficiency, prior PCI or prior medication (except for ACE inhibitor and angiotensin receptor blocker). Also the differences in age and gender were non-significant.

Outcome of patients with respect to the GI is shown in Table 2. Patients with NG had the highest 30-day mortality (15,6%) followed by G3I (14.8%) and G2I (6.8%). *p*-Value for the difference was 0.003. 30-day cardiovascular (CV) mortality was 14.8%, 12.3% and 6.4% in the respective groups ($p = 0.007$). 30-day MACE occurred in 23.0% of the patients with NG, 22.2% of G3I and 13.4% of G2I ($p = 0.013$). Patients with NG had the highest and those with G2I the lowest in-hospital ($p < 0.001$) and 1-year ($p < 0.001$) mortality. The maximum troponin T level was highest in the G3I group and lowest in the G2I group.

In the Kaplan-Meier curve (Fig. 5), G2I stands out as the ECG marker with the best outcome early on; G3I and NG have similar high early mortality. After the first 90 days, the decline in survival is steeper in NG than in G3I. *p*-Value for the difference between the three groups is <0.001.

Table 3 shows the results of logistic regression univariate and multivariable analyses. In the univariate analysis, G3I (OR 2.00, 95% CI 1.07–3.72, $p = 0.029$) and NG (OR 2.95, 95% CI 1.79–4.84, $p < 0.001$) were associated with increased 1-year mortality as compared to G2I. In the multivariable analysis, G3I (OR 2.36, 95% CI 0.924–6.03, $p = 0.073$) had a tendency towards and NG (OR 2.82, 95% CI 1.36–5.85, *p*

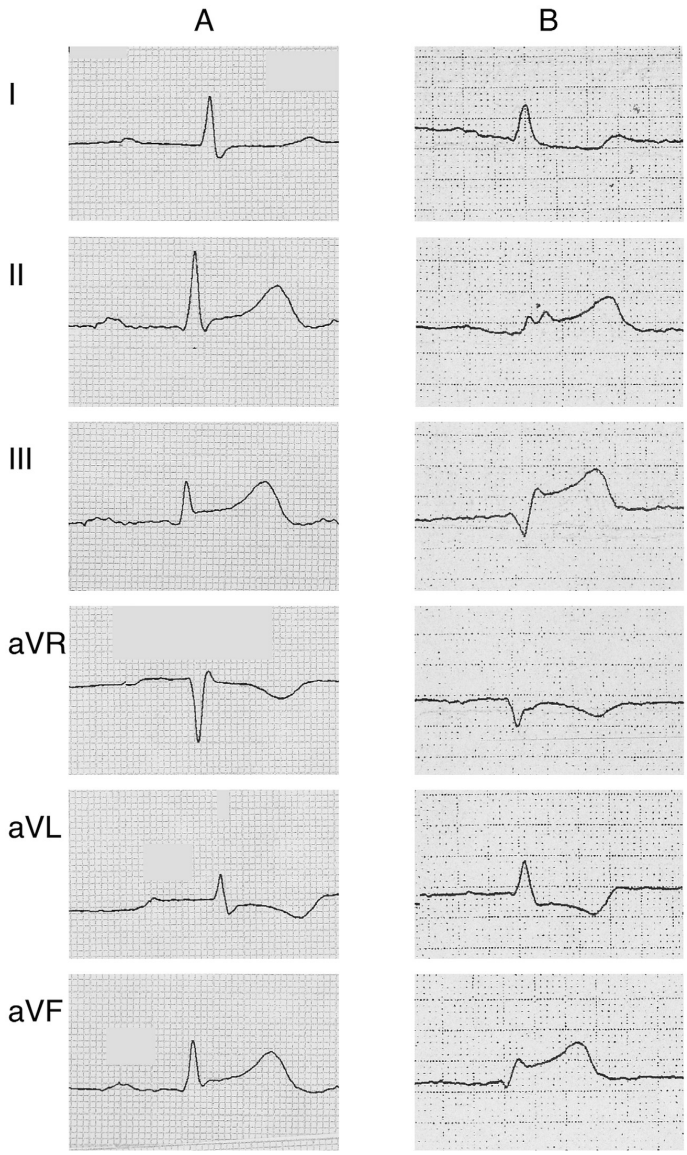

Fig. 2. Grade 2 ischemia (Panel A) and Grade 3 ischemia (Panel B) in inferior STEMI (50 mm/s). In a qR type complex, G3I is shown as ST-elevation >50% of the height of the R-wave.

$= 0.005$) was associated with increased 1-year mortality. Other variables significantly associated with increased 1-year mortality in the multivariable analysis were age and Killip class >1.

Discussion

In our all-comers study, in-hospital, 30-day and 1-year mortality was more than twice as high in G3I as in G2I. Our results align with previous studies, which, contrary to the present study, almost without exception included non-ECG related exclusion criteria, such as limits for time from symptom onset, age, previous MI, and excess bleeding risk. In the DANAMI-2 trial, where both FT and pPCI were used, 30-day mortality for G3I and G2I was 9.7% vs. 4.8%, respectively [4]. Also in another large study ($n = 2.603$), almost the double in-hospital mortality was found in G3I compared with G2I [18]. In the Thrombolysis in Myocardial Infarction 4 trial, mortality was even three times higher in patients with G3I than in those with G2I [6].

Previous studies on grades of ischemia have clearly demonstrated the adverse outcome of G3I but they may have excluded a wide range of potentially high-risk STEMI patients. Our all-comers study confirmed the relatively benign course of G2I, but also identified a clearly high-risk group, namely STEMI patients, for whom ischemia grading does not apply. The patients with NG showed the highest mortality in short-term and mid-term follow-up. This patient group has not been well

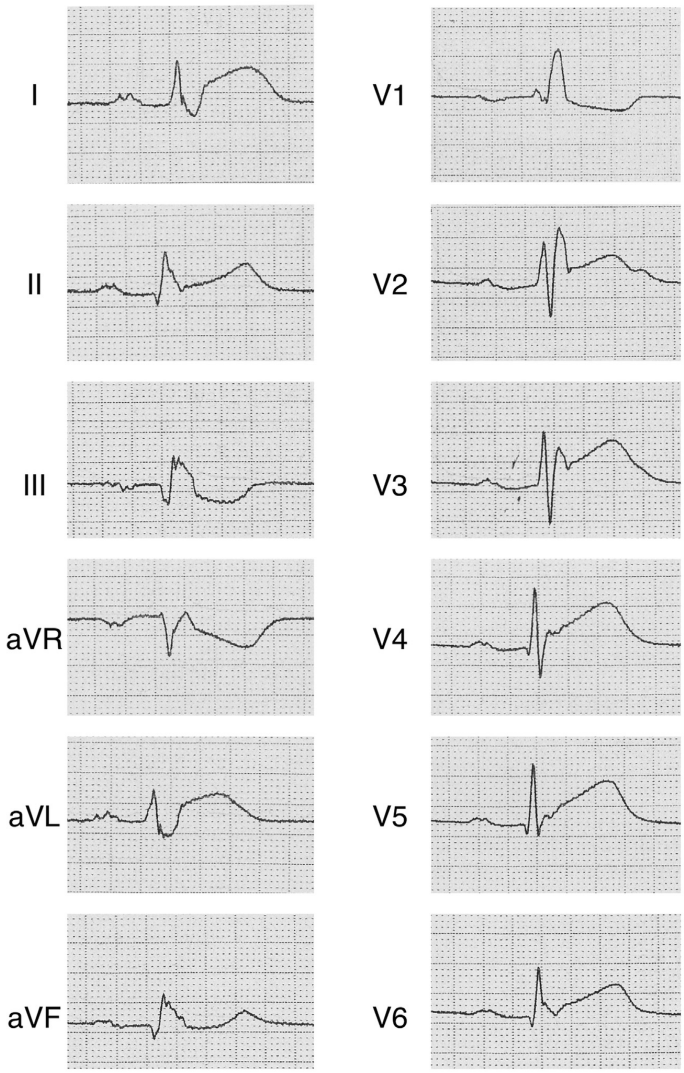

Fig. 3. An example of a patient in the "No grade" group. Anterior STEMI with QRS > 120 ms due to right bundle branch block (50 mm/s).

established in the literature. In the DANAMI-2 study, the patients excluded from ischemia grading had 12.6% 30-day mortality, as compared to 9.7% in G3I and 4.8% in G2I. Within the 253 excluded patients, however, there were 48 patients with missing ECG, 11 with incomplete ECG and 11 with no ST elevation [4]. Thus the excluded patients were not directly comparable with the NG group of the present study.

The NG group in the present study comprised patients with T-wave inversions or a broad QRS complex. Patients with NG more often had prior congestive heart failure than G2I or G3I. This is understandable, because bundle branch block or other intraventricular conduction defect is often seen in heart failure [19]. In acute STEMI, QRS duration is known to affect outcome [13]. In patients with coronary artery disease, a wider QRS is associated with sudden cardiac arrest [20]. NG patients also more often had a history of prior CABG compared with the other groups, evidently reflecting more severe coronary disease. Longer delays from symptom onset to ECG and to treatment logically lead to later stages of the infarct process, which can be expressed as T-wave inversion in the presenting ECG – the most frequent ECG pattern in the NG group. These patients may have less potential for saving ischemic myocardium from injury with reperfusion therapy [21]. T-wave inversions in the baseline ECG in STEMI predict high mortality at least in late-presenting patients [14,22]. NG is probably not a uniform patient group but a cluster of ECG patterns associated with poor outcome. It is plausible that NG represents either a later stage of the infarct process with less potential to save myocardium by reperfusion therapy or an infarct in a structurally abnormal heart.

Of the three groups in this study, the patients with G3I seemed to have the largest infarcts as reflected by the highest maximum troponin level. Despite lower maximum troponin levels, NG patients had similar poor early outcome in the Kaplan-Meier analysis (Fig. 5). Perhaps a smaller infarct in a structurally altered heart results in as poor outcome as a larger infarct in a previously healthy heart. Survival analysis also

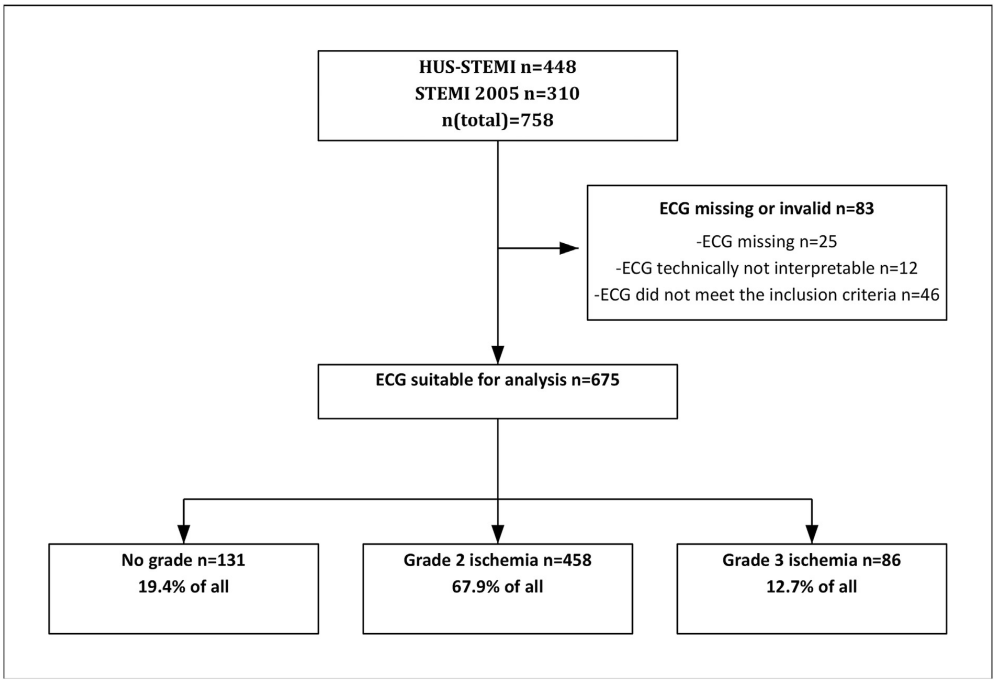

Fig. 4. Number of patients included in the groups No grade, Grade 2 ischemia and Grade 3 ischemia.

Table 1
Baseline characteristics based on ECG ischemia grading (NG = no grade). Location of the STEMI and pathologic Q waves were not determined in patients with NG.

	NG	*n* = 135	G2I	*n* = 458	G3I	*n* = 86	
	%	*n*	%	*n*	%	*n*	*p* Value
Male	62.6	82	64.4	295	74.4	64	0.154
Current smoker	29.4	35	37.1	161	36.3	29	0.297
Diabetes	25.2	33	17.1	78	18.6	16	0.108
Hyperlipidaemia	40.5	53	47.4	217	39.5	34	0.204
Hypertension	56.9	74	56.3	258	47.7	41	0.307
Prior STEMI	16.3	21	9.9	45	8.2	7	0.082
Prior angina	31.1	37	27.6	121	28.4	23	0.750
Prior CHF	12.4	16	5.2	24	1.2	1	0.001
Prior TIA/stroke	11.5	15	7.2	33	7.0	6	0.268
Renal insufficiency	6.9	9	2.4	11	3.5	3	0.045
Prior PCI	9.2	12	5.5	25	7.0	6	0.301
Prior CABG	10.7	14	2.6	12	1.2	1	<0.001
Killip class > 1	46.6	61	26.1	119	32.9	28	<0.001
Pathological Q-waves			20.3	93	38.4	33	
STEMI in anterior location			45.6	209	46.5	40	
ASA	36.2	47	28.4	130	23.5	20	0.105
Clopidogrel	3.1	4	0.9	4	1.2	1	0.153
Warfarin	6.2	8	5.2	24	3.5	3	0.686
β Blocker	38.5	50	31.9	146	24.1	20	0.088
Calcium channel blocker	20.0	26	16.6	76	12.9	11	0.392
Statin	24.8	32	19.9	91	16.3	14	0.283
ACEi/ARB	34.6	45	23.9	109	22.4	19	0.036
pPCI	42.7	56	33.6	154	29.1	25	0.075
FT	32.1	42	56.8	260	62.8	54	<0.001
NRT	25.2	33	9.6	44	8.1	7	<0.001
	NG		G2I		G3I		
	Median	Quartiles	Median	Quartiles	Median	Quartiles	*p* Value
Age (years)	69.5	58.9–78.6	65.5	56.7–76.0	66.8	55.3–76.8	0.267
Time from symptom onset to ECG (minutes)	172	69.0–380	80.0	41.0–172	75.0	42.3–182	<0.001
Time from symptom onset to treatment (minutes)	286	144–556	150	91.0–248	110	72.0–215	<0.001

STEMI = ST elevation myocardial infarction, CHF = congestive heart failure, TIA = transient ischemic attack, PCI = percutaneous coronary intervention, pPCI = primary PCI, CABG = Coronary artery bypass graft, ACEi = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, pPCI = primary PCI, FT = fibrinolytic therapy, NRT = No reperfusion therapy within 4 h from presentation.

Table 2
Outcome based on the grade of ischemia.

	NG		G2I		G3I		*p* Value
	%	*n*	%	*n*	%	*n*	
30-Day follow-up		122		439		81	
Mortality	15.6	19	6.8	30	14.8	12	0.003
CV mortality	14.8	18	6.4	28	12.3	10	0.007
AMI	6.6	8	4.6	20	6.2	5	0.610
Stroke	0.8	1	1.6	7	3.7	3	0.284
New non-elective CABG/PCI	2.5	3	3.0	13	2.5	2	0.939
MACE	23.0	28	13.4	59	22.2	18	0.013
Lost for follow-up		9		19		5	
Mortality		131		458		86	
In-hospital	16.0	21	5.2	24	11.6	10	<0.001
1-year	25.2	33	10.3	47	18.6	16	<0.001
	NG median	Quartiles	Grade 2 median	Quartiles	Grade 3 median	Quartiles	*p* Value
Maximum troponin	2.72	1.00–5.38	1.87	0.463–5.15	3.93	1.02–8.22	0.001

CV = cardiovascular, AMI = acute myocardial infarction, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, MACE = major adverse cardiovascular endpoints.

shows that mortality in G2I and G3I remains low after the first 90 days, whereas mortality in NG is higher. This may reflect the higher mortality of patients with heart failure independent of the STEMI.

Both G3I and NG were associated with increased 1-year mortality as compared to G2I in the logistic regression univariate analysis. In NG, the association was more distinct. In the multivariable analysis, NG was independently associated with increased 1-year mortality, as compared to G2I. In G3I, there was a tendency towards association with increased 1-year mortality ($p = 0.073$). Our study indicates that G2I can be used as a reliable predictor of relatively favorable outcome in STEMI. On the other hand, NG reliably predicts poor outcome. G3I patients have high in-hospital, 30-day and 1-year mortality as compared to G2I, but in real life G2I and NG may be better prognostic indicators than G3I. Interestingly, in another real life study, Zalenski et al. [23] found no significant association between G3I and 2-year mortality. Their study population did not comprise STEMI patients exclusively and the number of included patients was quite low ($n = 229$).

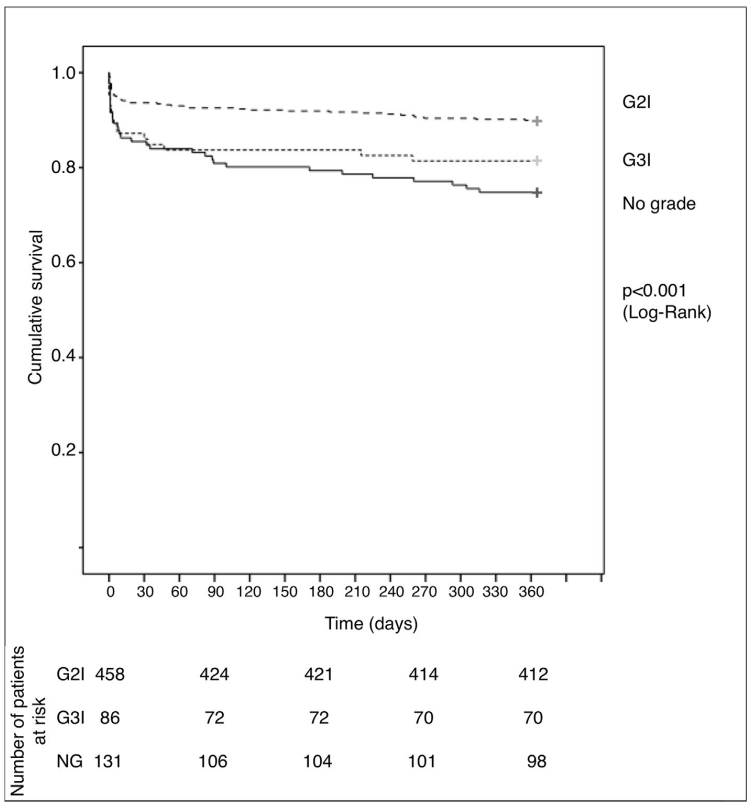

Fig. 5. Kaplan-Meier curve showing the 1-year survival of the patients with NG, G2I and G3I.

Table 3
Logistic regression univariate and multivariable analyses with 1-year mortality as the endpoint.

	Univariate analysis			Multivariable analysis		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Grade of ischemia						
G2I	Ref.			Ref.		
G3I	2.00	1.07–3.72	0.029	2.36	0.924–6.03	0.073
No grade	2.95	1.79–4.84	<0.001	2.82	1.36–5.85	0.005
Male	0.450	0.291–0.697	<0.001	1.26	0.632–2.50	0.514
Age	1.09	1.07–1.11	<0.001	1.05	1.02–1.09	0.002
Current smoker	0.489	0.269–0.890	0.019	1.31	0.584–2.95	0.511
Diabetes	2.63	1.63–4.25	<0.001	1.82	0.854–3.88	0.121
Hyperlipidaemia	0.595	0.379–0.935	0.024	0.579	0.286–1.17	0.129
Hypertension	1.94	1.22–3.08	0.005	1.50	0.620–3.62	0.369
Prior STEMI	1.24	0.639–2.40	0.527			
Prior angina	2.00	1.21–3.28	0.007	1.69	0.885–3.23	0.112
Prior CHF	5.64	2.91–10.9	<0.001	1.45	0.455–4.62	0.529
Prior TIA/stroke	3.15	1.69–5.87	<0.001	1.79	0.663–4.82	0.251
Renal insufficiency	8.91	3.79–21.0	<0.001	1.40	0.325–6.02	0.653
Prior PCI	1.41	0.635–3.15	0.397			
Prior CABG	1.39	0.514–3.77	0.516			
Killip class > 1	9.71	5.89–16.0	<0.001	5.83	2.91–11.7	<0.001
Time from symptom onset to ECG	1.00	1.00–1.00	0.443			
Time from symptom onset to treatment	1.00	1.00–1.00	0.826			
Pathological Q-waves	1.82	1.14–2.90	0.013	1.65	0.812–3.34	0.167
STEMI in anterior location	1.27	0.825–1.96	0.278			
Reperfusion therapy						
NRT	Ref.			Ref.		
FT	0.341	0.195–0.599	<0.001	1.05	0.397–2.75	0.929
pPCI	0.294	0.158–0.546	<0.001	0.980	0.369–2.60	0.968
ASA	2.16	1.39–3.37	0.001	1.15	0.534–2.47	0.722
Clopidogrel	3.11	0.765–12.7	0.113			
Warfarin	2.23	1.01–4.91	0.048	0.881	0.226–3.44	0.855
β blocker	3.04	1.95–4.75	<0.001	1.36	0.645–2.87	0.419
Calcium channel blocker	2.47	1.50–4.06	<0.001	1.69	0.761–3.75	0.197
Statin	1.21	0.722–2.04	0.465			
ACEi/ARB	1.63	1.02–2.60	0.042	0.635	0.293–1.37	0.248

For abbreviations, see Table 2.

Although no firm conclusions can be drawn from the present study about the exact reasons for poor outcome in the NG patients, it is possible that the effect of therapeutic measures is more limited in these patients than in those with G2I and G3I.

The present study is the first one to report the incidence of G2I and G3I in a STEMI population without (non-ECG) exclusion criteria. The rate of G3I proved to be lower than in most previous studies, where the proportion usually has been between 20% and 50% [4,7,18]. We have no definite explanation for the low number of patients with G3I in our study. The previous publications usually represent either retrospective analysis of randomized trials of FT or pPCI, or single center studies of consecutive patients. There was wide variation in the exclusion and inclusion criteria between the studies. Due to the potential bleeding risks with FT, randomized trials with these agents had the most exclusion criteria. One could speculate that mostly G2I patients were excluded.

The definition of the GI may explain some of the differences in the relative proportions of G2I and G3I. Like in our study, most investigators excluded patients with inverted T waves, but investigators have used different definitions for T-wave inversion. In our study, only T-wave inversion in the lead(s) with maximal ST elevation resulted in exclusion, while in some studies, any T-wave inversion in a lead with ST-segment elevation resulted in study exclusion [18]. Most previous authors define G3I as absence of an S wave below the isoelectric line in leads V1–V3 (leads that usually have a terminal S wave) or a J-point amplitude ≥50% of the R-wave amplitude in all other leads. This definition was also used in the present study. However, other definitions exist; Lee et al. [24] interpreted leads V1–V3 as qR type in the presence of Q waves and absence of S-waves. According to our definition, leads V1–V3 are by default rS type and disappearance of S-waves in those leads should always be interpreted as G3I in anterior wall STEMI. Garcia-Rubira et al. [25] only used the criterion of J-point/R-wave ratio >0.5 in all leads for QRS distortion, ignoring the disappearance of S waves in V1–V3. They did not mention excluding ECGs with T wave inversion either [25].

Conclusion

In our all-comers study, STEMI patients not eligible for ischemia grading due to broad QRS or inverted T waves, proved to have higher mortality than those without these ECG characteristics. We also found that G2I on the presenting ECG results in survival benefit regarding short- and mid-term mortality in comparison with other STEMIs. The present study implies that STEMI is a group of different diseases instead of one uniform disease. In the future it would be interesting to study whether these groups benefit from different treatment strategies.

Limitations

There are some limitations to be reported in our study. The study population consists of two sub-studies with differences in reperfusion therapy. However, the distribution of GIs was similar in the two studies. As the distribution is similar, the study results are relevant for the whole study population.

At the time of the studies, troponin T was the most widely used biochemical marker of myocardial injury. In some hospitals, troponin I was used and, hence, 52 patients had to be excluded from the troponin analyses.

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Declaration of interest

None.

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PUBLICATION II

Comparison of the prognostic role of Q waves and inverted T waves in the presenting ECG of STEMI patients.

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ORIGINAL ARTICLE

WILEY

Comparison of the prognostic role of Q waves and inverted T waves in the presenting ECG of STEMI patients

Kimmo Koivula[1,2] | Kjell Nikus[2,3] | Juho Viikilä[4] | Jyrki Lilleberg[5] | Heini Huhtala[6] | Yochai Birnbaum[7] | Markku Eskola[2,3]

[1]South Karelia Central Hospital, Lappeenranta, Finland

[2]Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

[3]Department of Cardiology, Heart Center, Tampere University Hospital, Tampere, Finland

[4]Cardiology, Helsinki University Central Hospital, Helsinki, Finland

[5]Department of Internal Medicine, Hyvinkää Hospital, Hyvinkää, Finland

[6]Faculty of Social Sciences, University of Tampere, Tampere, Finland

[7]The Section of Cardiology, The Department of Medicine, Baylor College of Medicine, Houston, Texas

Correspondence
Kimmo Koivula, South Karelia Central Hospital, Valto Käkelän katu 1, 53130 Lappeenranta, Finland.
Email: kimmo.koivula@helsinki.fi

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Abstract

Background: Both Q waves and T-wave inversion (TWI) in the presenting ECG are associated with a progressed stage of myocardial infarction, possibly with less potential for myocardial salvage with reperfusion therapy. Combining the diagnostic information from the Q- and T-wave analyses could improve the prognostic work-up in ST-elevation myocardial infarction (STEMI) patients.

Methods: We sought to determine the prognostic impact of Q waves and TWI in the admission ECG on patient outcome in STEMI. We formed four groups according to the presence of Q waves and/or TWI (Q+TWI+; Q–TWI+; Q+TWI–; Q–TWI–). We studied 627 all-comers with STEMI derived from two patient cohorts.

Results: The patients with Q+TWI+ had the highest and those with Q–TWI– the lowest 30-day and one-year mortality. One-year mortality was similar between Q–TWI+ and Q+TWI–. The survival analysis showed higher early mortality in Q+TWI– but the higher late mortality in Q–TWI+ compensated for the difference at 1 year. The highest peak troponin level was found in the patients with Q+TWI–.

Conclusion: Q waves and TWI predict adverse outcome, especially if both ECG features are present. Q waves and TWI predict similar one-year mortality. Extending the ECG analysis in STEMI patients to include both Q waves and TWI improves risk stratification.

KEYWORDS
ECG, Q wave, STEMI, T-wave inversion

1 | INTRODUCTION

The risk of death varies among patients with ST-elevation myocardial infarction (STEMI). Specific risk scores have been developed to improve risk assessment. The TIMI (thrombolysis in myocardial infarction) risk score applies clinical data to assess the risk of death (Morrow et al., 2000). ECG-based risk scores were introduced to aid in the assessment of acuteness of the ischemic process (Wilkins et al., 1995) and the area at risk (Aldrich et al., 1988). However, the presenting ECG in STEMI provides prognostic tools without need for complex analyses. The Sclarovsky-Birnbaum grading of ischemia classifies STEMI patients into two categories according to the distortion of the terminal portion of the QRS complex: grade 3 ischemia predicts higher short- and mid-term mortality and a larger infarct with a higher thrombus burden and more microvascular damage (Birnbaum, Birnbaum, & Birnbaum, 2014). However, this score applies only to patients with positive T waves in the leads with ST elevation. Another "at-a-glance" classification of STEMI is simply based on the analysis of Q and T waves in the ECG at presentation. "Evolving myocardial infarction" (EMI) is defined as pathological Q waves and/or inverted T waves, while these changes are absent in the "Pre-infarction syndrome" (PIS) (Sclarovsky, 1999). In the DANAMI-2 trial, patients with PIS had more advantage of primary percutaneous coronary intervention (pPCI) than of fibrinolytic

therapy (FT), while in the patients presenting with the EMI pattern, there was no significant difference between the two therapies (Eskola et al., 2007). The prognostic role of Q waves and T-wave inversions (TWI) in acute MI has been separately investigated in several studies. Q waves are the hallmark of myocardial necrosis, but they may also represent reperfusion (Blumenthal, Wang, & Pang, 1975; Horan, Flowers, & Johnson, 1971; Savage, Wagner, Ideker, Podolsky, & Hackel, 1977). Q waves predicted nonpatency of the culprit artery (Wong et al., 1999), a larger infarct (Delewi et al., 2013; Raitt et al., 1995) and higher 30-day and one-year mortality (Birnbaum et al., 1997; Siha et al., 2012; Wong et al., 2006). Post-treatment TWI in STEMI was associated with culprit artery patency and a favorable outcome (Corbalan et al., 1999; Doevendans et al., 1995; Lee et al., 2017; Matetzky et al., 1994; Ophuis et al., 2000; Sgarbossa et al., 2000), possibly indicating myocardial reperfusion. However, inverted T waves in the presenting ECG have been associated both with patency (Hira, Moore, Huang, Wilson, & Birnbaum, 2014) and nonpatency (Wong et al., 1999) of the culprit artery. Combining the diagnostic information from the Q- and T-wave analyses could improve the prognostic work-up in STEMI patients. Accordingly, the aim of this study was to establish the prognostic role of Q waves and TWIs in a real-life STEMI population.

2 | METHODS

This study comprises two Finnish nonrandomized STEMI populations. The STEMI 2005 study was conducted in the region of the Tampere University Hospital with a population of ~1.2 M. Data on the incidence, demographics, treatment strategies and delays were collected for consecutive STEMI patients (n = 310) in four hospital districts during a six-month period (Nikus et al., 2008). Regarding reperfusion therapy, both pPCI and FT were used. The study was observational, and treatment choices were based on prevailing international and regional guidelines.

In the HUS-STEMI study, patients (n = 448) were included during one year (2007–2008) in the district of the Helsinki University Central Hospital (Viikila et al., 2013). The study was observational, and the choice of reperfusion therapy was based on the decision by a consulting cardiologist. FT was recommended for hemodynamically stable patients when the time from symptom onset to treatment was ≤3 hr. As in the STEMI 2005 study, use of ancillary anti-thrombotic therapy and other therapeutic decisions were based on prevailing guidelines.

There were no prespecified exclusion criteria in the two studies. The inclusion criteria were as follows:

Acute chest pain/discomfort and

1. ST-elevations of ≥0.2 mV in at least 2 of the leads V1–3 or
2. ST-elevations of ≥0.1 mV in at least 2 other contiguous leads (V4–6; I, aVL; II, III, aVF) or
3. New or presumably new left bundle branch block.

We used troponin T with a cutoff <0.01 μg/L. Renal insufficiency was defined as creatinine >150 μM (1.70 mg/dl) on admission.

A written informed consent was signed by the patients before enrolment. The local Ethics Committees approved the study protocol.

For the present study, mortality data were collected from the official national registry (Statistics Finland), which records 100% of deaths of Finnish citizens at home and nearly 100% abroad. Regarding other endpoints, data from the two studies were used.

The primary endpoint was mortality at one year. Other prespecified endpoints were in-hospital mortality, 30-day mortality, and 30-day MACE (major adverse cardiovascular events: a composite of cardiovascular death, stroke, re-infarction and new, unplanned revascularization procedures).

The definition of "no revascularization therapy" (NRT) was: no FT or angiography within 4 hr from presentation.

The ECG data were analyzed by one investigator (KK), who at the time of the analysis was blinded to clinical data. In case of doubt, a mutual agreement was sought with two senior cardiologists (ME, KN). We found that in 46 patients the ST changes did not meet the established cutoff values, although included by the investigators on-site. These patients were excluded. Likewise, patients with a missing/incomplete (n = 25), or noninterpretable ECG (n = 8) were excluded. Patients with a wide QRS (>120 ms) were excluded as well (n = 52) (Figure 1).

Pathological Q waves were defined according to the Third Universal Definition of Myocardial Infarction (Thygesen et al., 2012). Any TWI ≥0.05 mV was considered as inverted. Q waves and TWIs outside the leads with maximum ST elevation were ignored. We formed four groups according to the presence of Q waves and/or TWIs (Q+TWI+, Q−TWI+, Q+TWI−, and Q−TWI−) (Figure 2).

The data were analyzed with SPSS Statistics 25. We compared the four groups with respect to different prespecified variables. In categorical variables, we used the χ^2 test or when applicable, Fisher's exact test. The distribution of all continuous variables was skewed, so we used median values and the independent-samples Mann–Whitney U test for the difference between the two groups. Interquartile ranges were defined using the weighted average. We performed a logistic regression univariate analysis using one-year mortality as the endpoint. We present odds ratios with 95% confidence intervals (CI). We selected the variables with a p value <0.1 to the multivariable analysis.

3 | RESULTS

The Q+TWI+ pattern was found in 29 patients (4.6%), Q−TWI+ in 50 patients (8.0%), Q+TWI− in 130 patients (20.7%) and Q−TWI− in 418 patients (66.7%) (Figure 1). The distribution of the four groups was similar in the STEMI 2005 and HUS-STEMI studies (p = 0.304).

The baseline characteristics of the four ECG categories are shown in Table 1. The Q+TWI+ group clearly had the highest proportion of males (82.8%), as the proportion in the other three groups was 44.0%–67.7% (p = 0.003). The proportion of patients with

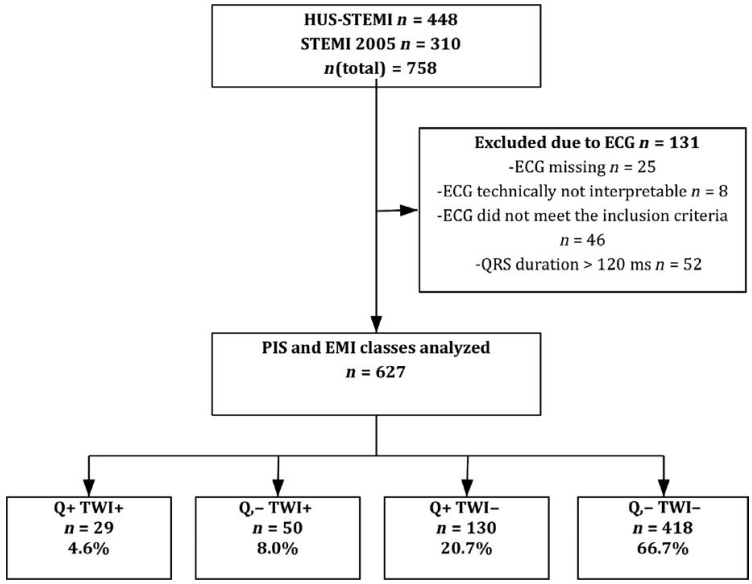

FIGURE 1 The number of included and excluded patients and the number of patients in the four ECG groups

diabetes was highest in Q+TWI+ (34.5%) and lowest in Q–TWI– (15.6%), $p = 0.033$. Killip class >1 was seen more often in the groups with Q waves (44.8% in Q+TWI+ and 39.5% in Q+TWI–) as compared to those with no Q waves (30.0% in Q–TWI+ and 23.8% in Q–TWI–), $p = 0.001$. Likewise the location of the STEMI more often was anterior in the groups with Q waves ($p < 0.001$) with the highest proportion in the Q+TWI– group (76.9%).

There was no significant difference between the groups in the rate of pPCI. However, FT more often was given to the patients with no TWI (55.4% in Q+TWI– and 58.4% in Q–TWI–) as compared to those with TWI (24.1% in Q+TWI+ and 28.0% in Q–TWI+), $p < 0.001$. Also, the proportion of patients who received no immediate reperfusion therapy differed between the groups being highest in Q+TWI+ (34.5%) and lowest in Q–TWI– (8.4%), $p < 0.001$. There was no significant difference in the use of medication between the groups.

Time from symptom onset to ECG was longest in the patients with TWI (365 min in Q+TWI+ and 184 min in Q–TWI+) and shortest in those with no TWI (89 min in Q+TWI– and 73 min in Q–TWI–), $p < 0.001$. The time from symptom onset to treatment was 498, 320, 153, and 142 min in the respective groups, $p < 0.001$.

Patient outcome according to the ECG categories is shown in Table 2. Thirty-day mortality was highest in patients with Q+TWI+, followed by Q+TWI–, Q–TWI–, and finally Q–TWI+ (20%, 14.4%, 6.8% and 6.4%, respectively, $p = 0.012$). One-year mortality was 31%, 19.2%, 9.8%, and 22% in the respective groups ($p < 0.001$). One-year mortality did not differ between the Q+TWI– and Q–TWI+ patients ($p = 0.677$, not shown in the tables).

The highest peak troponin levels were found in patients with Q+TWI– (3.23 μg/L), followed by Q+TWI+ (2.81 μg/L), Q–TWI+ (2.59 μg/L) and Q–TWI– (1.81 μg/L), p value for the difference was 0.002. In the Kaplan–Meier survival analysis, the patients with Q+TWI+ had the worst outcome early-on (Figure 3). Patients with Q+TWI– and those with Q–TWI+ had similar one-year survival. The survival curves indicate high early mortality in the former group while in the latter group late mortality was higher. p Value for the difference in survival between the four groups was <0.001 (Log-Rank).

The results of the logistic regression analyses are shown in Table 3. In the logistic regression univariate analysis, all other groups were associated with higher one-year mortality as compared to Q–TWI–. In the multivariable analysis, Q+TWI+ was independently associated with one-year mortality (OR 7.14, 95%CI 2.05–24.9, $p = 0.002$), while Q+TWI– was not (OR 1.46, 95%CI 0.614–3.54, $p = 0.385$), and Q–TWI+ had a tendency toward independent association (OR 3.13, 95%CI 0.900–10.9, $p = 0.073$). Other variables independently associated with one-year mortality were age, hyperlipidemia, and Killip class >1.

4 | DISCUSSION

Q waves and inverted T waves have been recognized as ECG markers of a progressed stage of myocardial infarction since the dawn of STEMI diagnostics. The prognosis of the combination of Q waves and/or TWI (evolving myocardial infarction, EMI) was studied in the DANAMI-2 trial, where this ECG pattern was an independent risk factor for the composite endpoint of mortality, clinical infarction, and disabling stroke (Eskola et al., 2007). The present study is the first one to compare the prognosis of Q waves and TWI.

In the present study, Q waves and TWI showed different prognostic features. The patients with both Q waves and TWI had the worst outcome. One-year mortality was similar in patients with either Q+TWI– or Q–TWI+. Interestingly, the Kaplan–Meier analysis

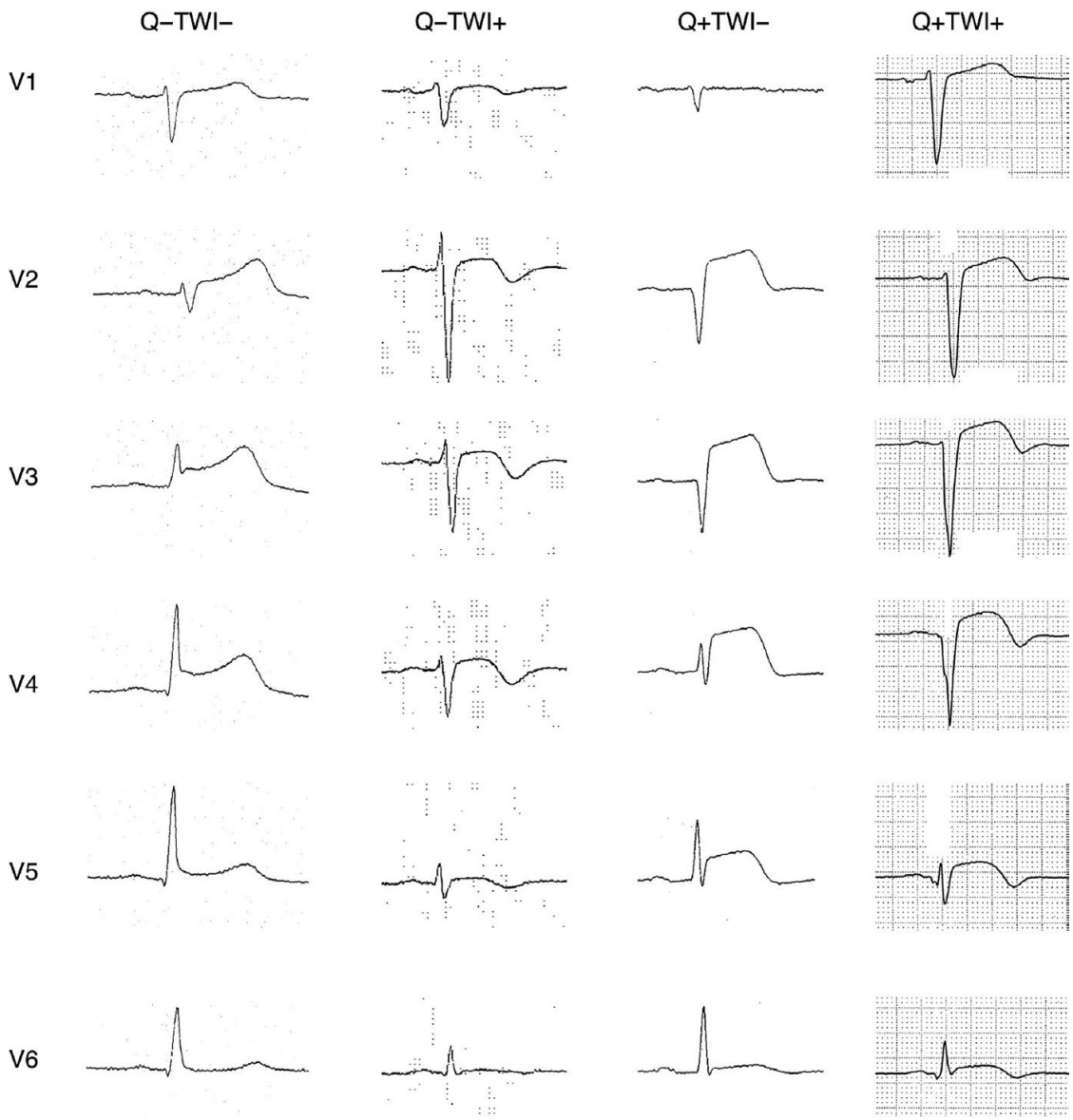

FIGURE 2 The four ECG groups showed in anterior STEMI (50 mm/s)

showed high early mortality in Q+TWI− and high late mortality in Q-TWI+. According to peak troponin values, patients with Q waves had larger infarcts, which could explain high early mortality. The relatively high late mortality of the Q−TWI+ group is more difficult to explain.

The immediate ECG changes caused by acute coronary artery occlusion are a positive, prominent T wave and ST elevation, features which qualify for the Q−TWI− classification (or preinfarction syndrome) (Nikus et al., 2010). Q waves and inverted T waves are mostly considered as later changes during the infarct process with less potential for myocardial salvage. However, our results imply that Q waves and TWI are different phenomena despite comparable outcome at one-year follow-up. Basically, TWI is seen in late-presenting STEMI patients, whereas Q waves imply a large infarct. Killip class was higher in patients with Q waves. As Q waves indicate more extensive myocardial damage, their association with higher Killip class is logical. Thus, a patient with both Q waves and TWI may often be a late-presenter with a large infarct. It is plausible that

TABLE 1 Baseline characteristics

	Q+TWI+ *n* = 29 *n* (%)	Q−TWI+ *n* = 50 *n* (%)	Q+TWI− *n* = 130 *n* (%)	Q−TWI− *n* = 418 *n* (%)	*p* Value
Gender (male)	24 (82.8)	22 (44.0)	88 (67.7)	273 (65.3)	0.003
Current smoker	14 (51.9)	13 (28.3)	44 (37.6)	148 (37.0)	0.254
Diabetes	10 (34.5)	10 (20.0)	29 (22.3)	65 (15.6)	0.033
Hyperlipidemia	11 (37.9)	15 (30.0)	64 (49.2)	188 (45.0)	0.113
Hypertension	16 (57.1)	22 (44.0)	79 (60.8)	223 (53.3)	0.206
Prior STEMI	5 (17.2)	3 (6.0)	18 (14.1)	35 (8.4)	0.093
Prior angina	10 (35.7)	14 (31.8)	30 (25.2)	115 (28.5)	0.663
Prior CHF	2 (7.1)	4 (8.0)	6 (4.6)	20 (4.8)	0.591
Prior TIA/stroke	2 (6.9)	4 (8.0)	7 (5.4)	32 (7.7)	0.846
Renal insufficiency	2 (6.9)	2 (4.0)	3 (2.3)	11 (2.6)	0.387
Prior PCI	1 (3.4)	5 (10.0)	9 (6.9)	22 (5.3)	0.461
Prior CABG	2 (6.9)	2 (4.0)	2 (1.5)	12 (2.9)	0.264
Killip class >1	13 (44.8)	15 (30.0)	51 (39.5)	99 (23.8)	0.001
STEMI in anterior location	16 (55.2)	23 (46.0)	100 (76.9)	150 (35.9)	<0.001
pPCI	12 (41.4)	24 (48.0)	41 (31.5)	139 (33.3)	0.143
FT	7 (24.1)	14 (28.0)	72 (55.4)	244 (58.4)	<0.001
NRT	10 (34.5)	12 (24.0)	17 (13.1)	35 (8.4)	<0.001
Aspirin	11 (37.9)	13 (26.0)	45 (34.6)	105 (25.2)	0.112
Clopidogrel	1 (3.4)	1 (2.0)	2 (1.5)	3 (0.7)	0.188
Warfarin	0 (0.0)	3 (6.0)	5 (3.8)	23 (5.5)	0.625
β-blocker	7 (24.1)	19 (38.0)	45 (34.9)	122 (29.3)	0.356
Calcium channel blocker	3 (10.3)	11 (22.0)	22 (16.9)	66 (15.8)	0.578
Statin	9 (31.0)	7 (14.0)	27 (20.8)	79 (18.9)	0.301
ACEi/ARB	11 (37.9)	15 (30.0)	35 (26.9)	93 (22.4)	0.172
	Median (quartiles)	**Median (quartiles)**	**Median (quartiles)**	**Median (quartiles)**	
Age (years)	65 (54–72)	68 (58–77)	65 (55–78)	66 (57–76)	0.831
Time from symptom onset to ECG (min)	356 (80–730)	184 (72–465)	89 (45–208)	73 (40–161)	<0.001
Time from symptom onset to treatment (min)	498 (285–940)	320 (235–795)	153 (94–299)	142 (85–240)	<0.001

Note. ACEi: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; CABG: coronary artery bypass graft; CHF: congestive heart failure; FT: fibrinolytic therapy; NRT: no reperfusion therapy; PCI: percutaneous coronary intervention; pPCI: primary PCI; STEMI: ST-elevation myocardial infarction; TIA: transient ischemic attack.

this combination represents the STEMI category with the worst outcome in our classification.

In the present study, the proportion of anterior STEMI differed between the four ECG categories being highest in the patients with Q waves. Both Q waves (Wong et al., 2006) and inverted T waves (Hira et al., 2014) have been reported more often in the anterior leads. A high proportion of anterior STEMI in the EMI group was also reported in the DANAMI-2 trial (Eskola et al., 2007). There is no evidence for myocardial necrosis to develop faster in the anterior wall. We think that the criteria are more sensitive for anterior Q waves, and this also is possibly true for TWI. There may also be other differences in the typical evolving ECG patterns in STEMI of different locations.

In individual patients, myocardial necrosis progresses at different rates. Collateral flow and ischemic preconditioning are known to alleviate the ischemic damage (Ottani et al., 1995). Hence, the time from symptom onset may not be the best way to assess the evolution of the infarct process; ECG scoring systems, such as the Anderson-Wilkins score, may provide more accurate information (Sejersten et al., 2007).

The pathophysiologic role of Q waves in STEMI is controversial. In canine experiments, Q waves appeared only after the release of the coronary occlusion and seemed to indicate both myocardial reperfusion and damage (Blumenthal et al., 1975; Bodenheimer, Banka, Levites, & Helfant, 1976). Wong et al found Q waves to be

TABLE 2 Outcome with respect to Q waves and T-wave inversion (for abbreviations, see Table 1)

	All *n* (%) *n* = 627	Q+TWI+ *n* (%) *n* = 29	Q−TWI+ *n* (%) *n* = 50	Q+TWI− *n* (%) *n* = 130	Q−TWI− *n* (%) *n* = 418	*p* Value
Thirty-day follow-up						
Thirty-day CV mortality	47 (7.9)	4 (16.0)	3 (6.4)	14 (11.2)	26 (6.5)	0.126
Thirty-day AMI	29 (4.9)	2 (8.0)	2 (4.3)	7 (5.6)	18 (4.5)	0.705
Thirty-day stroke	11 (1.8)	0 (0)	0 (0)	4 (3.2)	7 (1.8)	0.655
Thirty-day new nonelective CABG/PCI	15 (2.5)	0 (0)	0 (0)	2 (1.6)	13 (3.3)	0.578
Thirty-day MACE	90 (15.1)	6 (24.0)	4 (8.5)	25 (20.0)	55 (13.8)	0.108
Lost for follow-up	31	4	3	5	19	
In-hospital mortality	45 (7.2)	5 (17.2)	4 (8.0)	12 (9.2)	24 (5.7)	0.077
1-year mortality	86 (13.7)	9 (31.0)	11 (22.0)	25 (19.2)	41 (9.8)	<0.001
	All Median (quartiles)	**Q+TWI+ Median (quartiles)**	**Q−TWI+ Median (quartiles)**	**Q+TWI− Median (quartiles)**	**Q−TWI− Median (quartiles)**	***p* Value**
Maximum troponin µg/L	2.17 (0.588–5.38)	2.81 (1.31–4.59)	2.59 (0.750–4.78)	3.23 (0.930–8.80)	1.81 (0.425–4.67)	0.002

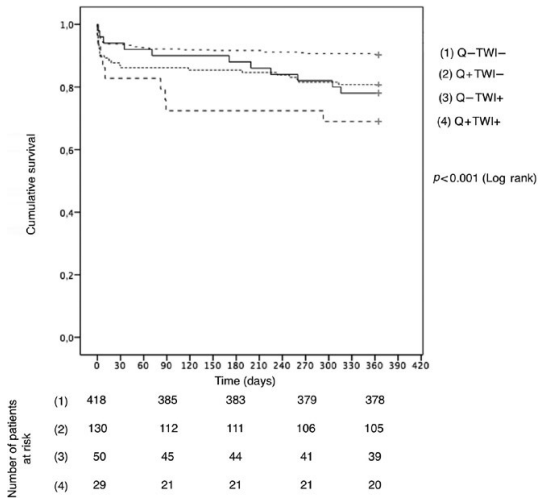

FIGURE 3 The Kaplan–Meier analysis showing the survival of patients with Q–TWI−, Q+TWI−, Q–TWI+, and Q+TWI+ in one-year follow-up

associated with nonpatency of the infarct-related artery (Wong et al., 1999). In the study of Raitt et al, abnormal Q waves were seen in 53% of the patients presenting within 1 hr from symptom onset, which makes their association with myocardial necrosis questionable, although Q waves did predict larger final infarct size (Raitt et al., 1995). Q waves may be associated with a larger area at risk. In cardiac magnetic resonance imaging, Q waves were a better indicator of infarct size than of infarct transmurality (Moon et al., 2004). Baseline Q waves have been shown to predict slower ST resolution even when the culprit artery is patent and the patients presents early, perhaps reflecting microvascular damage (Wong et al., 2002). Logically, higher mortality with Q waves has been reported in patients treated with FT (Wong et al., 2006) or primary PCI (Siha et al., 2012). Like previous studies, our study showed larger infarcts in the patients with Q waves.

Also the issue of inverted T waves in the ECG in STEMI is somewhat controversial. In patients presenting with ST elevations, development of negative T waves (or terminally inverted T waves) post-treatment is undoubtedly a predictor of favorable outcome, indicating culprit artery patency and reduced short-term mortality in patients treated with FT (Corbalan et al., 1999; Doevendans et al., 1995; Matetzky et al., 1994; Ophuis et al., 2000; Sgarbossa et al., 2000) or primary PCI (Lee et al., 2017). The role of TWI in the presenting ECG in STEMI is less obvious. In STEMI patients treated with pPCI, better myocardial recovery was reported with inverted T waves (Sorensen et al., 2009). In the HERO-1 study, inverted T waves in the presenting ECG were associated with nonpatency of the culprit artery (Wong et al., 1999). Contradictory, in the study by Hira et al., TWI in the presenting ECG predicted infarct-related artery patency with a median delay from symptom onset of 5 hr. Alsaab et al., (2014 also found an association between inverted T waves and culprit artery patency in a study with very short time delays: 50% of the patients with TWI had PCI within 1 hr from the symptom onset. In these studies, mortality was not assessed. In the study of Herz et al, TWI in the presenting ECG was a predictor of worse outcome in the late-presenting (>2 hr) patients, while in the early presenters, there was a tendency toward favorable outcome (Herz et al., 1999). Shimada, Po, Kanei, and Schweitzer (2013) found more in-hospital major adverse cardiac events, longer hospital stay and less ST resolution after PCI in patients with TWI. Although the mean delay to treatment was very long (28 hr) in

TABLE 3 Logistic regression univariate and multivariable analyses with one-year mortality as the endpoint

	Univariate analysis			Multivariable analysis		
	OR	95% CI	*p* Value	OR	95% CI	*p* value
ECG						
Q−TWI−	Ref.			Ref.		
Q+TWI−	2.19	1.27–3.77	0.005	1.46	0.614–3.54	0.385
Q−TWI+	2.59	1.23–5.45	0.012	3.13	0.900–10.9	0.073
Q+TWI+	4.14	1.77–9.68	0.001	7.14	2.05–24.9	0.002
Male	0.436	0.275–0.690	<0.001	1.72	0.782–3.765	0.179
Age	1.10	1.07–1.13	<0.001	1.06	1.02–1.10	0.001
Current smoker	0.495	0.265–0.924	0.027	1.07	0.442–2.59	0.881
Diabetes	2.65	1.59–4.40	<0.001	1.56	0.687–3.53	0.289
Hyperlipidemia	0.497	0.304–0.811	0.005	0.413	0.183–0.930	0.033
Hypertension	1.895	1.17–3.07	0.009	2.03	0.756–5.43	0.160
Prior STEMI	1.65	0.837–3.24	0.149			
Prior angina	1.94	1.14–3.29	0.014	1.24	0.603–2.54	0.561
Prior CHF	8.62	4.12–18.0	<0.001	1.43	0.402–5.07	0.582
Prior TIA/stroke	3.20	1.62–6.30	<0.001	1.66	0.549–5.00	0.370
Renal insufficiency	11.2	4.21–29.8	<0.001	1.79	0.316–10.1	0.512
Prior PCI	0.982	0.372–2.59	0.971			
Prior CABG	2.51	0.871–7.22	0.088	1.86	0.288–12.1	0.514
Killip class >1	10.8	6.39–18.3	<0.001	5.99	2.83–12.1	<0.001
Time from symptom onset to ECG	1.00	0.999–1.00	0.911			
Time from symptom onset to treatment	1.00	0.999–1.00	0.887			
STEMI in anterior location	1.41	0.894–2.22	0.14			
NRT	Ref.			Ref.		
FT	0.374	0.204–0.687	0.002	1.39	0.449–4.31	0.567
pPCI	0.353	0.182–0.684	0.002	1.25	0.397–3.92	0.705
Aspirin	2.35	1.47–3.76	<0.001	1.63	0.714–3.70	0.247
Clopidogrel	2.55	0.487–13.4	0.267			
Warfarin	2.31	0.998–5.35	0.050	1.24	0.284–5.44	0.772
β-blocker	3.24	2.02–5.18	<0.001	1.57	0.704–3.48	0.272
Calcium channel blocker	2.17	1.27–3.70	0.005	1.23	0.504–3.01	0.648
Statin	1.02	0.577–1.81	0.938			
ACEi/ARB	1.64	1.00–2.70	0.050	0.521	0.218–1.24	0.141

Note. For abbreviations, see Table 1.

the patients with TWI, the results were similar in the patients presenting early (<2 hr).

It seems that TWIs in the presenting ECG and those developing post-treatment have different outcome. In the presenting ECG, TWI indicates a later stage of the infarct with worse outcome—at least in the late-presenting patients. TWI post-treatment is a sign of reperfusion associated with favorable outcome. The present study parallels with former studies in showing higher mortality in STEMI patients with inverted T waves. In the present study, most of the TWI+ patients were late-presenters as defined in the study by Herz et al. (1999; median time from symptom onset to treatment 320–498 min in the TWI+ groups).

5 | LIMITATIONS

The study consisted of two study populations, which could result in nonuniformity. However, the design and the case report forms of the two studies were almost identical and the distribution of the studied ECG categories was similar in the two studies. Hence, these differences should not represent major obstacles regarding the interpretation of the study results.

At the time of the studies, some hospitals used troponin I instead of troponin T. Due to this fact, we had to exclude some (n = 49) patients from the analysis, which included troponin.

6 | CONCLUSION

Simply classifying STEMI patients into four categories based on Q- and T-wave analyses aids in outcome prediction. In all-comers, both Q waves and TWI predicted higher one-year mortality than ST elevations only. Q waves were associated with larger infarcts and TWIs with longer treatment delays. The patients with both Q waves and TWI had highest one-year mortality. Future studies in different patient populations and treatment strategies are required to better establish the role of this ECG classification in clinical routine practice.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

ORCID

Kimmo Koivula http://orcid.org/0000-0003-1227-7245

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PUBLICATION III

Long-term outcome of pre-specified ECG patterns in acute coronary syndrome.

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[a] Equal contributions

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Long-term outcome of pre-specified ECG patterns in acute coronary syndrome

Kimmo Koivula, MD [a,b,*,1], Kaari K. Konttila, BM [a,1], Markku J. Eskola, MD [c], Mika Martiskainen, MD [d], Heini Huhtala, MSc [e], Vesa K. Virtanen, MD [c], Jussi Mikkelsson, MD [f], Kati Järvelä, MD [g], Kari O. Niemelä, MD [c], Pekka J. Karhunen, MD [a,d], Kjell C. Nikus, MD [a,c]

[a] Faculty of Medicine and Health Technology, Tampere University, Finland
[b] South Karelia Central Hospital, Finland
[c] Heart Center, Department of Cardiology, Tampere University Hospital, Finland
[d] Fimlab Laboratories Tampere University Hospital, Tampere, Finland
[e] Faculty of Social Sciences, University of Tampere, Finland
[f] Heart Center, Satakunta Central Hospital, Pori, Finland
[g] Heart Center, Tampere University Hospital, Finland

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ABSTRACT

Background: Long-term outcome of real-life acute coronary syndrome (ACS) patients with selected ECG patterns is not well known.
Purpose: To survey the 10-year outcome of pre-specified ECG patterns in ACS patients admitted to a university hospital.
Methods: A total of 1184 consecutive acute coronary syndrome patients in 2002–2003 were included and followed up for 10 years. The patients were classified into nine pre-specified ECG categories: 1) ST elevation; 2) pathological Q waves without ST elevation; 3) left bundle branch block (LBBB); 4) right bundle branch block (RBBB) 5) left ventricular hypertrophy (LVH) without ST elevation except in leads aVR and/or V_1; 6) 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); 7) other ST depression and/or T wave inversion; 8) other findings and 9) normal ECG.
Results: Any abnormality in the ECG, especially Q waves, LBBB, LVH and global ischemia, had negative effect on outcome. In age- and gender adjusted Cox regression analysis, pathological Q waves (HR 2.28, 95%CI 1.20–4.32, $p = .012$), LBBB (HR 3.25, 95%CI 1.65–6.40, $p = .001$), LVH (HR 2.53, 95%CI 1.29–4.97, $p = .007$), global ischemia (HR 2.22, 95%CI 1.14–4.31, $p = .019$) and the combined group of other findings (HR 3.01, 95%CI 1.56–6.09, $p = .001$) were independently associated with worse outcome.
Conclusions: During long-term follow-up of ACS patients, LBBB, ECG-LVH, global ischemia, and Q waves were associated with worse outcome than a normal ECG, RBBB, ST elevation or ST depression with or without associated T-wave inversion. LBBB was associated with the highest mortality rates.

Introduction

Acute coronary syndrome (ACS) has poor long-term outcome [1,2]. However, mortality in ACS varies widely among patients. ECG is the cornerstone of early risk assessment in ACS due to its wide availability and good diagnostic yield [3].

ACS is usually classified as ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) or unstable angina (UA) according to ischemic symptoms in combination with ST deviations and cardiac troponin levels [4]. There are no ECG-related criteria for NSTEMI or UA except for the lack of ischemic ST elevations (STE). Patients with NSTEMI or UA may have a wide range of ECG changes that may affect their outcome. Some of these changes may reflect myocardial ischemia and some may imply underlying cardiac pathology. The ECG changes include Q waves, ST depression (ST-D), T-wave inversions (TWI), left ventricular hypertrophy (LVH), left bundle branch block (LBBB), right bundle branch block (RBBB) and global ischemia (GI). A patient with NSTEMI or UA may as well have a normal ECG.

Long- and short-term prognosis of many ECG patterns has been widely studied. However, knowledge about the long-term prognosis of normal vs. abnormal ECG in ACS is scarce. The aim of the present

* Corresponding author at: Kimmo Koivula South Karelian Central Hospital, Valto Käkelän katu 1, 53130 Lappeenranta, Finland.
E-mail address: kimmo.km.koivula@gmail.com (K. Koivula).
[1]Equal contributions.

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study was to assess the mortality rates of several pre-specified ECG patterns, including a normal ECG, during 10 years of follow-up in ACS patients.

Material and methods

The study protocol was previously described in detail [5]. TACOS is a real-life study of 1188 patients with acute coronary syndrome. The study was conducted in the region of Tampere University Central Hospital with a population of ~340.000. All consecutive patients with acute myocardial infarction (AMI) were recruited between 1 January 2002 and 31 March 2003. AMI was verified by elevated blood troponin (cTnI>0.2 μg/l). Troponin-negative patients with UA were recruited from 1 September 2002 to 31 March 2003. Patients discharged from the emergency department were not included. Also, the patients who died in the emergency department were excluded.

The study was observational. The treatment for each patient was chosen by the treating physician according to the regional, national and international guidelines.

Data were gathered by a study nurse and two investigators (ME and KjN). Follow-up started at the time point of the ECG used in the analysis and ended at the time of death or at the end of follow-up 31 January 2013. Median follow-up time of the survivors was 10.3 years (from 9.8 to 11.1 years). Mortality data were gathered from the Causes of Death register, maintained by Statistics Finland, which records 100% of deaths of Finnish citizens in Finland and nearly 100% abroad.

ECG

ECGs taken in the ambulance, referring health center or emergency department were screened for the study. For each patient, the acute stage ECG with maximal ischemic changes was chosen for the analysis. The patients were classified based on the ECG findings according to the QRST morphology as follows: STE; ST-D and/or TWI (ST-D/TWI); GI; Q wave; LBBB; RBBB; LVH; other ECG changes – and normal ECG. An example of each group is shown in Fig. 1.

STE was defined as ST-segment elevation in two adjacent leads: in leads V_{1-6} ⩾1.5 mm with ⩾2 mm in at least one lead, in leads II, III, aVF, I and aVL ⩾1 mm. The T-P interval was used as the reference line.

ST-D was defined as a negative shift of at least 0.5 mm from the baseline at the J-point in at least two contiguous leads. The cut-off for TWI was 0.5 mm. A biphasic T wave was defined as inverted, if the terminal portion of the wave was negative. Patients with ST-D were classified as GI in case of: ST-D ≥ 0.5 mm in ≥6 leads, maximally in leads V_{4-5} with inverted T waves and STE ≥0.5 mm in lead aVR.

In the Q wave group, STE fulfilling the abovementioned criteria were not allowed. The definition of pathological Q waves was: 1) in leads V_{1-3} any Q wave ⩾30 ms in duration; 2) in leads I, II, aVL, aVF, V_{4-6} Q wave ⩾1 mm deep and ⩾30 ms in duration in ⩾2 adjacent leads; and 3) in leads V_{1-2} R wave duration >40 ms and R/S ratio >1 in the absence of pre-excitation, right ventricular hypertrophy or right bundle branch block.

LBBB was defined as QRS ≥ 120 ms, broad and notched or slurred R waves in leads aVL, V_5, and V_6, absent Q waves in leads I, V_5, and V_6, and R-wave peak time prolongation of >60 ms in leads V_5 and V_6 [6].

RBBB was defined as 1) QRS ≥ 120 ms; 2) in leads V1 or V2 rsr′, rsR′ or rSR′ configuration OR normal R peak time in V5-V6 but >50 ms in V1 in the presence of pure dominant R wave in V1; 3) S wave duration greater than R wave duration or S wave duration >40 ms in leads I and V6.

For ECG-LVH two criteria were used, the Sokolow-Lyon voltage criteria: S wave in V1 + R wave in V5–6 > 35 mm and R-wave voltage >11 mm in lead aVL. ST-T changes secondary to LVH (ST-D in leads I, aVL, V5, V6 and STE in V1–V2) or other ST-D and/or TWI were included in this category.

The group of other ECG changes comprises patients with changes in their QRS complex or ST-T changes other than those mentioned above. These changes included intraventricular conduction defect ($n = 36$), ventricular paced rhythm ($n = 18$), ventricular rhythm ($n = 4$), ST changes not fulfilling the criteria for STE or ST-D (n = 3), high T waves ($n = 3$), pre-excitation ($n = 1$) and extreme left axis deviation ($n = 1$).

Normal ECG was defined as an ECG with normal QRST configuration. Left anterior and posterior fascicular blocks were included in the normal ECG group.

We excluded patients with missing ECG ($n = 1$) and heart rate > 130 ($n = 3$). The final study population comprises 1184 patients.

The ECGs were analyzed by three investigators (KjN, ME, KK).

Statistics

In the baseline characteristics, we present numbers of patients and percentages for categorical variables. Chi square is used for the

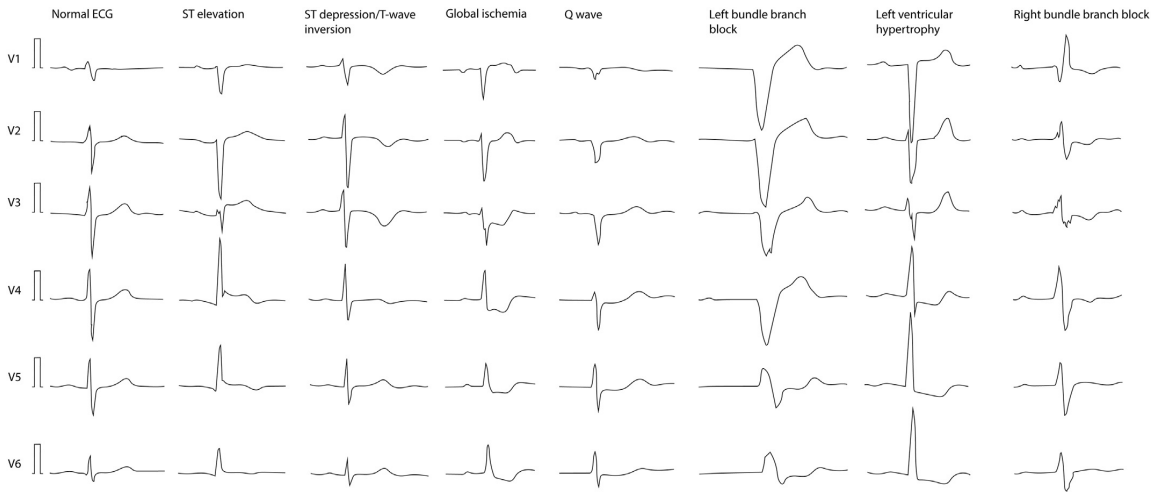

Fig. 1. An example of each ECG group (50mm/s). Precordial leads are shown.

statistical analyses in categorical variables. When applicable, we used Fisher's exact test. For continuous variables, we present median values with interquartile ranges (IQR). We used the Kruskal-Wallis test for the statistical analyses of continuous variables. Survival of patients in the different ECG groups is illustrated by a Kaplan-Meier curve, where the difference between the groups was tested with the Log Rank test. To adjust survival with age and gender, we performed forward stepwise Cox regression analysis. We present hazard ratios with 95% confidence intervals (CI). Statistical analyses were done with SPSS 25.

Ethics

All patients gave a written informed consent. The study protocol was approved by the Ethics Committee of Tampere University Hospital. The study was done according to the principles of Declaration of Helsinki.

Results

The baseline characteristics of each ECG group are shown in Table 1. Most patients were male (58.4%). The proportion of females differed among the groups being highest in GI (56.7%). Smoking was most common among patients with STE (24.9%) and least frequent among those with LBBB (5.1%). Hypertension was most common in the GI and LVH groups. Type 1 diabetes was infrequent in all groups (0–3.1%), while the proportion of type 2 diabetes varied between 15% (Normal ECG) and 34.9% (RBBB); the proportion was high in the LBBB (31.4%), other ECG changes (34.8%) and GI (30.2%) groups as well. The rate of prior AMI was highest in the Q wave (34.8%) and Other ECG changes (38.5%) groups and lowest in the Normal ECG group (10%). The ranges of in-hospital PCI and CABG were 4.2–24.6% and 3.0%–27.8%, respectively. Medications on admission and at discharge are shown in Table 1.

The median age of the study population was 72 years (IQR 63–80). Age differed remarkably among the ECG groups. The youngest patients were in the Normal ECG category (median 60, IQR 53–69) and the oldest in the GI (median 77, IQR 72–82), RBBB (median 77, IQR 71–83), LBBB and LVH (median 77, IQR 71–84 for both) categories. Median creatinine values varied between 74 (Normal ECG) and 103 μmol/l (Other ECG change). Median CRP values were between four (Normal ECG) and 22 (Q wave) mg/l. Systolic blood pressure was clearly highest in the LVH group (median 160, IQR 143–189).

The Kaplan-Meier curve (Fig. 2) shows the survival benefit of normal ECG compared to all other groups throughout the follow-up. The ECG groups STE and ST-D/TWI had similar long-term survival rates. The patients with RBBB, Q waves, other ECG changes, LVH, GI and LBBB had the lowest survival rates. The poor outcome of the patients with LBBB was evident from the beginning to the end of follow-up. The *p*-value for the difference between the groups is <0.001 (Log Rank).

To adjust survival with age and gender, we performed Cox regression analysis. The results are shown in Table 2. Adjusted survival was worst for LBBB (HR 3.25, 95% CI 1.65–6.40, $p = .001$). Other ECG groups with high mortality rates in the adjusted model were GI (HR 2.22, 95% CI 1.14–4.31, $p = .019$), Q waves (HR 2.28, 95%CI 1.20–4.32, $p = .012$), LVH (HR 2.53, 95% CI 1.29–4.97, $p = .007$) and other ECG changes (HR 3.01, 95% CI 1.56–6.09, $p = .001$). RBBB, STE and ST-D/TWI did not differ from normal ECG in the adjusted model.

Discussion

The present study of consecutive ACS patients evaluated the prognostic significance of several pre-specified ECG manifestations, including a normal ECG, at presentation. The pre-specified ECG groups had clear differences in their baseline characteristics and medication at hospital admission. It is not surprising that patients with Q waves in the ECG are more likely to have a history of previous AMI or that patients with ECG-LVH are more likely to have a history of hypertension. Therefore, each ECG pattern to some part reflects the complete patient profile instead of representing an independent phenomenon.

In the present study, a normal ECG predicted favorable outcome as compared to any studied QRST change. Normal ECG does not rule out ischemia or cardiac pathology but is a known predictor of favorable outcome in suspected AMI [7]. In the patients with normal ECG, 45% had elevated troponin levels. Ischemia may have resolved at the moment of the ECG recording or it may not be severe enough to be reflected in the ECG. It may also be that human eye is blind to subtle ischemic ECG changes. It was recently reported that deep neural network analysis reliably predicted death from an ECG considered normal by cardiologists in a large electronic health record database [8]. However, our results imply that normal ECG – as the human eye sees it – is a reliable predictor of favorable outcome in ACS.

STEMI is often considered the most acute and severe form of ACS. However, long-term outcome of STEMI does not go hand in hand with its bad reputation [1]. New STE in the ECG – especially with reciprocal ST-D – is usually due to acute coronary occlusion but STE may be caused by non-ischemic causes, such as pericarditis, early repolarization syndrome or Brugada syndrome [4]. Total occlusion of the culprit artery is more often seen in STEMI than in NSTEMI, while the opposite is true for multivessel disease [9–12]. It was somewhat surprising that the outcome of STE patients in the present study was almost as good as in those with a normal ECG; the same was true for ST-D/TWI. After adjusting with age and gender, STEMI patients did not have significantly higher 10-year mortality than those with a normal ECG (Table 2). The aforementioned difference in coronary disease severity may explain the relatively good outcome of STE. Especially compared with the patients with LBBB or GI, those presenting with STE less often had comorbidities such as hypertension or type 2 diabetes (Table 1). It is noteworthy that 8.3% of the patients with STE were troponin-negative. These patients did not have STEMI but most probably either more persistent or transient ST elevation with subsequently normal troponin levels. These troponin-negative patients contributed to the relatively favorable outcome of the STE group. As mentioned above, STE may also be caused by non-ischemic causes. However, patients with final diagnosis other than ACS were not included in this study.

ST-D and TWI often appear simultaneously in ACS patients. We therefore combined these ECG manifestations as one group. TWI may reflect many different conditions, but in patients with symptoms indicating ACS, ischemia is the likely cause [13,14]. A large registry data study showed that in-hospital mortality in NSTEMI patients with isolated TWI was lower than in those with a normal ECG [15]. Ischemic ST-Ds are thought to reflect regional subendocardial ischemia [16]. However, ST-D has low or moderate sensitivity and specificity for AMI [17]. In a study by Savonitto et al. ACS patients with ST-D had higher 6-month mortality than patients with STE. As compared to patients with both STE and ST-D, mortality was similar [11]. It is noteworthy that in that study, LBBB was classified as STE, and it is likely that the outcome of STE would have been even better without LBBB. In the present study, the outcome of ST-D/TWI patients was worse than in those with a normal ECG. However, in the Cox regression analysis, the difference was not statistically significant.

GI in the ECG typically reflects complex coronary artery disease, typically either left main or three-vessel disease [18,19]. Due to the complex disease, mortality is high in GI [20], and this was also the case in the present study. GI patients more often had elevated troponin levels (99%), and hypertension (62.5%) than the other groups (Table 1).

Q waves are traditionally thought to reflect myocardial necrosis and scar [21]. In the acute phase of ACS this may not always be the case. In STEMI, Q waves imply larger infarcts but they may be transient [22]. Q waves also imply higher risk of death in STEMI [23,24]. There is also study data indicating worse outcome in non-Q-wave MI than in Q-wave MI. [25]. It has to be pointed out that we excluded patients with STE from the Q-wave group. Therefore, our results cannot be directly compared with the results of studies comparing Q-wave and non-Q-

Table 1
Baseline characteristics based on ECG groups.

	Normal ECG n(%) n = 40	ST elevation n(%) n = 353	STD/TWI n(%) n = 160	Global ischemia n(%) n = 97	Q wave n(%) n = 272	LBBB n(%) n = 71	RBBB n(%) n = 43	LVH n(%) n = 82	Other ECG change n(%) n = 66	All n(%) n = 1184	p value
Female	14 (35.0)	128 (36.3)	83 (51.9)	55 (56.7)	91 (33.5)	37 (52.1)	15 (34.9)	43 (52.4)	41 (37.6)	492 (41.6)	<0.001
Smoking	8 (21.6)	83 (24.9)	30 (20.0)	10 (11.9)	55 (22.3)	3 (5.1)	3 (7.7)	9 (12.2)	3 (5.6)	204 (18.9)	<0.001
Hypertension	18 (45.0)	177 (50.3)	88 (55.7)	60 (62.5)	136 (50.7)	42 (59.2)	19 (45.2)	51 (62.2)	41 (62.1)	632 (53.8)	0.100
Diabetes											0.040
Type 1	0 (0)	2 (0.6)	1 (0.6)	3 (3.1)	3 (1.1)	0 (0)	1 (2.3)	0 (0)	2 (3.0)	12 (1.0)	
Type 2	6 (15.0)	77 (21.8)	35 (22.0)	29 (30.2)	67 (24.7)	22 (31.4)	15 (34.9)	15 (18.3)	23 (34.8)	289 (24.5)	
Prior AMI	4 (10.0)	53 (15.2)	28 (17.9)	30 (30.9)	93 (34.8)	19 (27.1)	13 (30.2)	21 (25.6)	25 (38.5)	286 (24.5)	<0.001
PCI	6 (15.0)	87 (24.6)	17 (10.6)	10 (10.3)	33 (12.1)	3 (4.2)	3 (7.0)	4 (4.9)	9 (13.6)	172 (14.5)	<0.001
CABG	4 (10.0)	26 (7.4)	10 (6.3)	27 (27.8)	27 (9.9)	5 (7.0)	4 (9.3)	6 (7.3)	2 (3.0)	111 (9.4)	<0.001
TnI positive	18 (45.0)	324 (91.8)	113 (70.6)	96 (99.0)	234 (86.0)	60 (84.5)	34 (79.1)	68 (82.9)	47 (71.2)	994 (84.0)	<0.001
Medication at admission											
β blocker	16 (41.0)	142 (40.3)	87 (54.4)	65 (67.0)	135 (49.6)	35 (49.3)	22 (51.2)	45 (54.9)	38 (57.6)	585 (49.5)	<0.001
Diuretic	6 (15.4)	70 (19.9)	49 (30.6)	49 (50.5)	94 (34.6)	42 (59.2)	16 (37.2)	37 (45.1)	36 (54.5)	399 (33.8)	<0.001
Statin	9 (23.1)	65 (18.4)	47 (29.4)	26 (26.8)	55 (20.2)	14 (19.7)	8 (18.6)	17 (20.7)	20 (30.3)	261 (22.1)	0.121
ACE inhibitor	2 (5.1)	54 (15.3)	26 (16.3)	27 (27.8)	69 (25.4)	23 (32.9)	12 (27.9)	19 (23.2)	24 (36.4)	256 (21.7)	<0.001
ARB	4 (10.3)	19 (5.4)	13 (8.1)	5 (5.2)	21 (7.7)	6 (8.5)	1 (2.3)	11 (13.4)	3 (4.5)	83 (7.0)	0.232
ASA	19 (48.7)	124 (35.1)	72 (45.3)	54 (56.3)	124 (45.6)	32 (45.7)	20 (46.5)	41 (50.0)	41 (62.1)	527 (44.7)	0.001
Clopidogrel	1 (2.6)	4 (1.1)	2 (1.3)	1 (1.0)	2 (0.7)	1 (1.4)	1 (2.3)	0 (0)	0 (0)	12 (1.0)	0.888
Nitrate	19 (48.7)	118 (33.4)	75 (46.9)	69 (71.1)	128 (47.1)	48 (67.6)	24 (55.8)	44 (54.3)	39 (59.1)	564 (47.7)	<0.001
CCB	10 (25.6)	71 (20.2)	35 (21.9)	27 (27.8)	45 (16.5)	16 (22.5)	12 (27.9)	16 (19.5)	16 (24.2)	248 (21.0)	0.379
Digoxin	1 (2.6)	19 (5.4)	15 (9.4)	18 (18.6)	29 (10.7)	19 (26.8)	8 (18.6)	25 (30.5)	9 (13.6)	143 (12.1)	<0.001
Warfarin	1 (2.6)	21 (5.9)	17 (10.6)	15 (15.5)	38 (14.0)	17 (23.9)	5 (11.6)	12 (14.6)	17 (25.8)	143 (12.1)	<0.001
Medication at discharge											
β blocker	34 (85.0)	333 (94.3)	148 (92.5)	93 (95.9)	256 (94.1)	64 (90.1)	39 (90.7)	77 (93.9)	56 (84.8)	1100 (92.9)	0.067
Diuretic	13 (32.5)	157 (44.5)	80 (50.0)	87 (89.7)	187 (68.8)	59 (83.1)	28 (65.1)	63 (76.8)	45 (68.2)	719 (60.7)	<0.001
Statin	25 (62.5)	256 (72.5)	86 (53.8)	58 (59.8)	146 (53.7)	25 (35.2)	15 (34.9)	36 (43.9)	29 (43.9)	676 (57.1)	<0.001
ACE inhibitor	4 (10.0)	167 (47.3)	56 (35.0)	38 (39.2)	159 (58.5)	43 (60.6)	18 (41.9)	37 (45.1)	29 (43.9)	551 (46.5)	<0.001
ARB	4 (10.0)	21 (5.9)	16 (10.0)	6 (6.2)	22 (8.1)	5 (7.0)	1 (2.3)	10 (12.2)	4 (6.1)	89 (7.5)	0.446
ASA	35 (87.5)	332 (94.1)	141 (88.1)	80 (82.5)	241 (88.6)	55 (77.5)	34 (79.1)	71 (86.6)	51 (77.3)	1040 (87.8)	<0.001
Clopidogrel	9 (22.5)	115 (32.6)	29 (18.1)	16 (16.5)	43 (15.8)	6 (8.5)	5 (11.6)	9 (11.0)	7 (10.6)	239 (20.2)	<0.001
Nitrate	22 (55.0)	252 (71.4)	103 (64.4)	81 (83.5)	204 (75.0)	52 (73.2)	35 (81.4)	65 (79.3)	44 (66.7)	858 (72.5)	0.003
CCB	14 (35.0)	54 (15.3)	32 (20.0)	25 (25.8)	35 (12.9)	14 (19.7)	10 (23.3)	22 (26.8)	12 (18.2)	218 (18.4)	0.003
Digoxin	2 (5.0)	27 (7.6)	17 (10.6)	30 (30.9)	49 (18.0)	19 (26.8)	6 (14.0)	26 (31.7)	16 (24.2)	192 (16.2)	<0.001
Warfarin	4 (10.0)	58 (16.4)	33 (20.6)	22 (22.7)	90 (33.1)	28 (39.4)	7 (16.3)	25 (30.5)	21 (31.8)	288 (24.3)	<0.001
	Normal ECG median (IQR)	ST elevation median (IQR)	STD/TWI median (IQR)	Global ischemia median (IQR)	Q wave median (IQR)	LBBB median (IQR)	RBBB median (IQR)	LVH median (IQR)	Other ECG change median (IQR)	All median (IQR)	p value
Age	60 (53–69)	68 (56–77)	72 (59–79)	77 (72–82)	73 (64–80)	77 (71–84)	77 (71–83)	77 (71–84)	75 (69–79)	72 (63–80)	<0.001
Creatinine	74 (67–95)	84 (71–99)	81 (67–99)	92 (75–115)	90 (75–112)	100 (81–127)	84 (73–114)	90 (71–120)	103 (85–135)	87 (72–109)	<0.001
Maximum CRP	4 (2–9)	10 (3–37)	9 (2–50)	19 (4–67)	22 (5–69)	14 (5–67)	13 (4–100)	16 (4–68)	11 (3—33)	12 (3–57)	<0.001
Systolic BP	145 (133–168)	144 (126–166)	150 (132–172)	144 (122–170)	141 (121–161)	146 (124–160)	156 (137–187)	160 (143–189)	139 (117–163)	145 (126–167)	<0.001
Diastolic BP	84 (71–91)	80 (70–91)	80 (70–90)	77 (62–91)	81 (70–90)	79 (66–90)	78 (69–94)	83 (66–98)	76 (65–83)	80 (69–91)	0.093

AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; TnI = troponin I; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CRP=C-Reactive Protein; BP = blood pressure.

wave MI. Based on this, our Q-wave patient group probably consists of both "late comers" with a first ACS and those with an acute event "on top of" one or more old MIs (Table 1). In these patients, Q waves probably represent myocardial necrosis/scar rather than a great ischemic area at risk. This group of patients has not been well studied before. The 10-year mortality of patients with Q waves was nearly twice as high as in those with a normal ECG.

The left bundle branch of the cardiac conduction system is perfused via septal branches of the left anterior descending coronary artery and distal branches of the right or left circumflex coronary artery. Thus, new-onset LBBB may imply multivessel disease [26,27]. LBBB may imply underlying structural heart disease, which may have significant negative impact on patient outcome [28,29] both with [30,31] and without [32,33] ACS. The results for the present study confirm previous study results, but they also give new information; of several pre-specified ECG presentations, LBBB proved to be associated with the highest mortality rates during long-term follow-up.

The right bundle branch is perfused dominantly by branches of the left anterior descending artery (LAD) [34]. In the setting of ACS, RBBB may thus reflect infarct of the LAD territory. RBBB is a predictor of higher mortality in STEMI [35] and NSTEMI [36]. In a study by Widimsky et al., AMI patients with new or presumably new RBBB had higher in-hospital mortality than patients with LBBB or old RBBB. TIMI 0 flow of the infarct-related artery was more common in RBBB than in LBBB. [37] According to this study, ESC 2017 STEMI guidelines recommend considering invasive strategy in patients with ischemic symptoms and RBBB [38], although this was recently questioned [39]. Timoteo et al. found

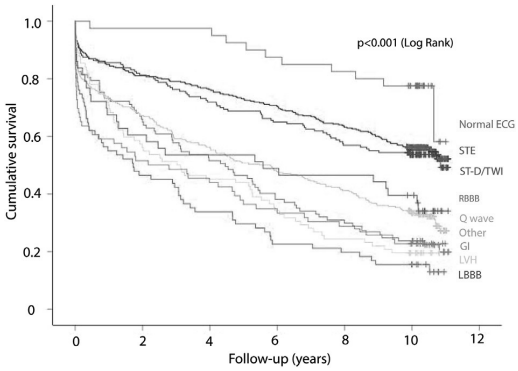

Fig. 2. The Kaplan–Meier analysis showing the survival of patients according to the ECG groups in ten-year follow-up.

Table 2
Cox regression. Adjusted hazard ratios for 10-year mortality are shown.

	HR	95% CI	p value
Normal ECG	Ref.	Ref.	Ref.
ST-D/TWI	1.45	0.74–2.81	0.277
STE	1.49	0.78–2.83	0.225
RBBB	1.84	0.89–3.82	0.100
GI	2.22	1.14–4.31	0.019
Q	2.28	1.20–4.32	0.012
LVH	2.53	1.29–4.97	0.007
Other ECG changes	3.01	1.56–6.09	0.001
LBBB	3.25	1.65–6.40	0.001
Age	1.07	1.06–1.08	<0.001
Gender (female)	0.90	0.77–1.06	0.199

ST-D = ST depression; TWI = T-wave inversion; STE = ST elevation; Q = Q wave; GI = global ischemia; LVH = left ventricular hypertrophy; LBBB = left bundle branch block.

higher one-year mortality in patients with RBBB than LBBB [40]. Contrary to that finding, the present study showed remarkably lower long-term mortality in RBBB than in LBBB. However, we didn't define RBBB as old or presumably new.

ECG-LVH may be caused by various cardiac conditions, such as hypertensive heart disease or aortic stenosis, all of which may affect the prognosis [41]. ECG criteria for LVH have low sensitivity but good specificity for left ventricular hypertrophy confirmed with autopsy or cardiac imaging [42–44]. ECG-LVH has been associated with poor prognosis both in patients with AMI [45] and in those without AMI [46]. Thus, ECG-LVH should be considered as a tool to assess prognosis rather than a tool to diagnose LVH. In the present study, the prognosis of patients with ECG-LVH was among the worst of the ECG categories.

The ECG group "Other" was associated with relatively poor long-term outcome and a high rate of comorbidity at baseline. As this was a heterogeneous group from the ECG point of view, it is difficult to draw any firm clinical conclusions of the significance of different ECG changes. The group included patients with broad QRS other than RBBB or LBBB. Previous studies have showed higher mortality in ACS patients with wider QRS [47,48]. In a study by Lev et al., ACS patients with undetermined ECG pattern had higher mortality and more comorbidities than patients with determined ECG pattern (STE or non-ST-elevation) [49]. However, LBBB was defined as undetermined ECG which may contribute to the poor prognosis.

Limitations

As with other studies, which have explored the long-term outcome of ACS patients, also this study has the limitations associated with changes in the treatment of ACS. The use of emergent and urgent invasive evaluation and of anti-thrombotic and statin treatment has changed a lot since the time when the study was performed. At the time of the study, in-hospital PCI was not routine treatment in ACS. Partly the low percentage is due to the all-comer nature of the study. Some patients may have been too old or co-morbid to be suitable candidates for coronary angiography.

Therefore, it is challenging to assess the long-term outcome of ACS. However, the difference in outcome between the different ECG manifestations is likely to prevail despite the changing treatment.

Conclusions

During 10-year follow-up of ACS patients, LBBB, ECG-LVH, GI, and Q waves were associated with worse outcome than a normal ECG, RBBB, STE or ST-D/TWI. LBBB was associated with the highest mortality rates.

Author statement

Kimmo Koivula: Writing – original draft, formal analysis, investigation, visualization; **Kaari K. Konttila**: coseptualization, investigation, visualization; **Markku J. Eskola**: conceptualization, writing - review & editing, supervision, project administration, funding acquisition; **Mika Martiskainen**: coseptualization, resources, writing - review & editing; **Heini Huhtala**: formal analysis; **Vesa K. Virtanen**: coseptualization, project administration; **Jussi Mikkelsson**: coseptualization, resources; **Kati Järvelä**: coseptualization, resources, writing - review & editing; **Kari O. Niemelä**: coseptualization, project administration; **Pekka J. Karhunen**: coseptualization, resources, writing - review & editing; **Kjell C. Nikus**: conceptualization, writing - review & editing, supervision, project administration, funding acquisition.

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Declaration of Competing Interest

None.

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