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JOONAS LEIVO

Use of the 12-Lead Electrocardiogram in Risk Assessment and in Selecting Thrombectomy for ST-Elevation Myocardial Infarction

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ABSTRACT

Different tools have been proposed for risk assessment in ST-elevation myocardial infarction, but they may not be optimally implemented in clinical practice. The Global Registry of Acute Coronary Events (GRACE) score is a recommended tool for assessing the risk of an adverse outcome in patients with STEMI. The GRACE score, however, utilizes only one crude ECG finding, ST elevation (STE), while it has been shown that the use of the ECG in the risk assessment of patients with a STEMI extends beyond STE. Along with STE, ECG findings contributing to an adverse outcome include pathological Q waves, T wave inversion (TWI) and the grade of ischemia (GI). STEMI patients can be stratified into different temporal stages with the use of Q waves and TWI. The ECG finding of STE without Q waves and TWI signifies preinfarction syndrome (PIS), and STE with Q waves and/or TWI signifies an evolving myocardial infarction (EMI). An EMI is thought to represent a later stage of the infarction process, and patients with an EMI have a poorer outcome than do patients with PIS. On the other hand, the severity of myocardial ischemia could be assessed from the ECG with different GIs. Grade 1 ischemia (G1I) is considered to be the first sign of myocardial ischemia in an acute total coronary artery occlusion and is defined as a positive, tall and peaked T wave. As the myocardial ischemia progresses, STE becomes evident, constituting G2I, and, finally, in a minority of patients, a distortion of the terminal portion of the QRS complex develops, marking the most severe form, G3I.

Aspiration thrombectomy has been used in conjunction with a primary percutaneous coronary intervention (pPCI) as a treatment for STEMI. Earlier studies indicated a benefit from aspiration thrombectomy in reducing the thrombus burden and preventing distal embolization and the no-reflow phenomenon. The trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) showed that routine aspiration thrombectomy did not lower the risk of an adverse outcome in the whole STEMI patient population. A safety concern was also raised with reference to the finding of an elevated risk of stroke associated with the use of the technique. Consequently, the current guidelines do not recommend routine use of thrombectomy.

The aims of the current study were to evaluate the prognostic significance of the PIS and EMI findings in an ECG (Study I); to assess the prognostic significance of the G2I and G3I findings in an ECG (Study II); to determine the joint and separate effect of Q waves and TWI on the outcome (Study III); and to determine whether any STEMI patients, as stratified into different risk groups according to Q waves, TWI and GI, would benefit from routine aspiration thrombectomy (Studies I, II and III).

Study I comprised 7,860 patients from the TOTAL trial, who were divided into PIS and EMI groups according to the ECG changes. It was shown that patients with EMI had a higher risk of the primary outcome, defined as a composite of cardiovascular (CV) death, cardiogenic shock, New York Heart Association (NYHA) class IV heart failure (HF), and recurrent MI, when compared to patients with PIS within 1-year follow-up, and the ECG classification (EMI vs PIS) was an independent predictor of an adverse outcome (adjusted HR 1.54; 95% CI 1.30–1.82; $p < 0.001$). Compared to the GRACE score alone, the EMI and PIS ECG patterns combined with the GRACE score were found to have significant incremental prognostic value. There was no difference in the effect of treatments (thrombectomy vs PCI alone) on the outcome among either EMI or PIS patients.

In study II, 7,211 patients from the TOTAL trial were included in the analysis. The patients were stratified into two groups based on their GI ECG classification (G2I and G3I). During 1-year follow-up, the patients with G3I had a higher risk of a primary outcome compared to the patients with G2I (9.8% vs 6.4%; aHR, 1.27; 95 % CI 1.04–1.55; $p = 0.022$), but there was no benefit from routine aspiration thrombectomy for either of the patient groups.

Study III enrolled 7,831 patients from the TOTAL trial. The patients were divided into four groups according to the findings of pathological Q waves and TWI: Q-TWI- (no Q waves and no TWI), Q+TWI-, Q-TWI+, and Q+TWI+. Q waves and TWI were also analysed separately. Patients with the Q+TWI+ pattern were at the highest risk of a primary outcome compared to patients with the Q-TWI- pattern, but this was only seen within the time period of 40 days' follow-up (aHR 2.10; 95% CI 1.45–3.04; $p < 0.001$). In patients with the Q+TWI- and Q+TWI+ patterns, there was no additive risk of a primary outcome after 40 days of follow-up. In contrast, patients with the Q-TWI+ pattern had a higher risk of a primary outcome than did patients with the Q-TWI- pattern only after 40 days (aHR 1.82; 95% CI 1.06–3.14; $p = 0.031$). In the separate analysis of Q waves and TWI, patients with Q waves had a higher risk of a primary outcome only within 40 days (aHR 1.80; 95% CI 1.48–2.19; $p < 0.001$), while patients with TWI had a higher risk of a primary

outcome only after 40 days (aHR 1.63; 95% CI 1.04–2.55; p = 0.033). There was no benefit from routine aspiration thrombectomy in any of the Q/TWI patient groups, not even when patients with Q waves and TWI were analysed separately.

In conclusion, risk assessment in patients with a STEMI can be achieved reliably based on the ECG at presentation by analysing the presence of Q waves, TWI and QRS distortion (G3I). The implementation of Q waves and TWI in addition to the GRACE score improves prognostic assessment compared to the GRACE score alone. The routine use of aspiration thrombectomy in conjunction with pPCI does not lower the risk of an adverse outcome even in high-risk subgroup of patients assessed according to the ECG changes. There is currently no effective way outside of the guideline-based therapeutic measures to influence the outcome of STEMI patients who are at the highest risk of an adverse outcome. Future studies should consider an ECG-based risk stratification when assessing potential treatment tailoring for patients with a STEMI.

TIIVISTELMÄ

ST-nousuinfarktin (*ST-elevation myocardial infarction*, STEMI) riskin arvioimiseen on kehitetty erilaisia työkaluja, mutta niiden käyttö kliinisessä työssä ei ole toteutunut optimaalisesti. STEMI-potilaiden riskin arvioimiseen on suositeltu GRACE-riskilaskuria. Se ottaa huomioon kuitenkin vain yhden sydänsähkökäyrän (EKG) muuttujan, ST-nousun, vaikka EKG:hen perustuvan riskiarvion on osoitettu olevan laajennettavissa myös muihin EKG-muuttujiin. ST-nousun lisäksi myös patologisten Q-aaltojen, negatiivisten T-aaltojen (*T-wave inversion*, TWI) ja iskemia-asteen on havaittu vaikuttavan ennusteeseen. Q-aaltojen ja T-inversioiden perusteella STEMI-potilaat voidaan jakaa ajallisesti eri vaiheisiin. EKG-löydöstä, jossa ei nähdä ST-nousun lisäksi Q-aaltoja tai T-inversioita, kutsutaan preinfarktisyndroomaksi (PIS) ja löydöstä, jossa ST-nousun lisäksi on Q-aallot ja/tai T-inversiot, kehittyväksi sydäninfarktiksi (*evolving myocardial infarction*, EMI). EMI-muutoksen on ajateltu edustavan myöhempää ST-nousuinfarktin vaihetta, ja EMI-potilailla on todettu olevan huonompi ennuste verrattuna PIS-potilaisiin. Sydänlihasiskemian vaikeusastetta voidaan toisaalta arvioida iskemia-asteluokituksen (*grade of ischemia*, GI) avulla. Ensimmäisen asteen iskemian (G1I) on ajateltu olevan ensimmäinen merkki sydänlihasiskemiasta akuutin sepelvaltimotukoksen yhteydessä, ja se nähdään EKG:ssä korkeana, piikkimäisenä T-aaltona. Sydänlihasiskemian edetessä EKG:hen kehittyy ST-nousu, joka kuvaa toisen asteen iskemiaa (G2I). Pienellä osalla potilaista iskemia etenee vaikeimmaksi, kolmannen asteen iskemiaksi (G3I), jonka EKG-löydöksenä havaitaan QRS-kompleksin loppuosan vääristymä (”distorsio”).

Aspiraatiotrombektomiaa (trombi-imu) on käytetty yhdessä primaari-PCI:n (*primary percutaneous coronary intervention*, pPCI) kanssa STEMIn hoidossa. Aiemmissa tutkimuksissa oli havaittu trombi-imun olevan hyödyllinen trombikuorman vähentämisessä sekä distaalisen embolisaation ja no reflow -ilmiön estämisessä. TOTAL-tutkimuksessa kuitenkin osoitettiin, että rutiininomainen trombi-imu ei parantanut ennustetta yleisessä STEMI-potilaiden otoksessa, ja toisaalta sen huomattiin lisäävän aivoinfarktiriskiä. Tämän seurauksena nykyiset hoitosuositukset eivät suosittele trombi-imun rutiininomaista käyttöä.

Tämän väitöskirjatutkimuksen tarkoituksena oli arvioida PIS- ja EMI-muutosten ennusteellista merkitystä (Osajulkaisu I); arvioida iskemia-asteluokittelun (G2I ja

G3I) merkitystä riskin arvioinnissa (Osajulkaisu II); määrittää Q-aaltojen ja T-inversioiden merkitys ennusteen kannalta sekä yhdessä että erikseen (Osajulkaisu III); sekä selvittää, hyötyvätkö Q-aaltojen, T-inversioiden ja iskemia-asteen mukaisiin riskiryhmiin jaetut STEMI-potilaat rutiininomaisesta trombi-imusta (Osajulkaisut I, II ja III).

Osajulkaisu I koostui 7 860 potilaasta, jotka osallistuivat TOTAL-tutkimukseen, ja heidät jaettiin EKG-muutoksiin perustuen PIS- ja EMI-ryhmiin. Tutkimuksessa osoitettiin, että EMI-potilailla oli vuoden seurannassa suurempi yhdistelmäpäävastemuuttujan (sydän- ja verisuonitautikuolema, sydänperäinen sokki, NYHA IV-luokan sydämen vajaatoiminta ja uusiutuva sydäninfarkti) riski verrattuna PIS-potilaisiin ja että kyseinen EKG-muutos (EMI vs. PIS) oli itsenäinen riskitekijä huonommalle ennusteelle (korjattu HR 1,54; 95 % luottamusväli [lv], 1,30–1,82; $p < 0,001$). EMI- ja PIS-EKG-muutokset yhdistettynä GRACE-riskilaskuriin lisäsivät riskinarviointikykyä pelkkään GRACE-riskilaskuriin verrattuna. EMI- ja PIS-potilaiden ennusteessa ei ollut eroa riippumatta siitä, tehtiinkö rutiininomainen trombi-imu vai pelkkä PCI.

Osajulkaisussa II analyysiin otettiin mukaan TOTAL-tutkimuksesta 7 211 potilasta, jotka jaettiin kahteen ryhmään perustuen iskemia-asteluokitteluun (G2I ja G3I). Potilailla, joilla havaittiin G3I, oli vuoden seurannassa suurempi riski päävastemuuttujalle verrattuna G2I-potilaisiin (9,8 % vs. 6,4 %; korjattu HR 1,27; 95 % lv 1,04–1,55; $p = 0,022$), mutta kumpikaan potilasryhmä ei hyötynyt rutiininomaisesta trombi-imusta.

Osajulkaisuun III otettiin mukaan 7 831 TOTAL-tutkimuksen potilasta. Heidät jaettiin neljään eri ryhmään patologisten Q-aaltojen ja T-inversioiden perusteella: Q-TWI- (ei Q-aaltoja, eikä T-inversioita), Q+TWI-, Q-TWI+ ja Q+TWI+. Patologisia Q-aaltoja ja T-inversioita tarkasteltiin myös erikseen. Potilailla, joilla havaittiin EKG-muutos Q+TWI+, oli suurempi päävastemuuttujan riski verrattuna potilaisiin, joilla oli EKG-muutos Q-TWI-, mutta riski oli suurentunut vain 40 päivän aikana seurantajakson alusta tarkasteltuna (korjattu HR 2,10; 95 % lv 1,45–3,04; $p < 0,001$). Potilailla, joilla todettiin EKG-muutos Q+TWI- tai Q+TWI+, päävastemuuttujan riski ei ollut enää suurentunut 40 päivän jälkeen. Sitä vastoin potilailla, joilla todettiin EKG-muutos Q-TWI+, päävastemuuttujan riski oli suurempi vasta 40 päivän jälkeen verrattuna potilaisiin, joilla oli EKG-muutos Q-TWI- (korjattu HR 1,82; 95 % lv 1,06–3,14; $p = 0,031$). Kun Q-aaltoja ja T-inversioita analysoitiin erikseen, havaittiin, että Q-aaltoja omaavien potilaiden päävastemuuttujariski oli suurentunut ainoastaan 40 päivän sisällä (korjattu HR 1,80; 95 % lv 1,48–2,19; $p < 0,001$) ja T-inversioita omaavilla potilailla vain 40 päivän

jälkeen (korjattu HR 1,63; 95 % lv 1,04–2,55; p = 0,033). Rutiininomaisesta trombi-imusta ei havaittu olevan hyötyä ennusteen kannalta missään potilasryhmässä, ei edes silloin, kun Q-aaltoja ja T-inversioita analysoitiin erikseen.

Yhteenvetona voidaan todeta, että STEMI-potilaiden riskiä voidaan arvioida luotettavasti diagnoosivaiheen EKG:stä analysoimalla patologisten Q-aaltojen, T-inversioiden ja QRS-kompleksin vääristymän (G3I) esiintymistä. GRACE-riskilaskuriin yhdistettynä tieto Q-aalloista ja T-inversioista parantaa riskinarvioimiskykyä. Rutiininomainen trombi-imu primaari-PCI:n yhteydessä ei paranna ennustetta edes niillä potilailla, joiden ennuste on EKG-muutosten perusteella jo lähtökohtaisesti huonompi. Nykyisten hoitosuositusten mukaisten menetelmien lisäksi tällä hetkellä ei ole tehokasta tapaa parantaa edes niiden STEMI-potilaiden ennustetta, joiden ennuste on kaikkein huonoin. Tulevaisuudessa STEMI-potilaiden hoidon räätälöintiin tarkoitetuissa tutkimuksissa tulisi ottaa huomioon EKG-muutoksiin perustuva riskinarviointi.

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ABBREVIATIONS

ACS	Acute coronary syndrome
AMI	Acute myocardial infarction
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CMR	Cardiac magnetic resonance (imaging)
CV	Cardiovascular
ECG	Electrocardiogram
EF	Ejection fraction
EMI	Evolving myocardial infarction
GI	Grade of ischemia
GRACE	Global Registry of Acute Coronary Events
FT	Fibrinolytic therapy
HF	Heart failure
HR	Hazard ratio
IDI	Integrated discrimination improvement
IMH	Intramyocardial haemorrhage
IRA	Infarct-related artery
IS	Infarct size
LAD	Left anterior descending coronary artery
LBBB	Left bundle branch block
LCx	Left circumflex coronary artery
LV	Left ventricle
LVEDP	Left ventricular end-diastolic pressure
MI	Myocardial infarction
MVO	Microvascular obstruction
NRI	Net reclassification index
PIS	Preinfarction syndrome
pPCI	Primary percutaneous coronary intervention
SPECT	Single-photon emission computed tomography

STEMI	ST-elevation myocardial infarction
STE	ST elevation
STD	ST depression
STR	ST resolution
TIMI	Thrombolysis In Myocardial Infarction
TnT/I	Troponin T/I
TOTAL	Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI
TVR	Target-vessel revascularisation
TWI	T wave inversion
UAP	Unstable angina pectoris

LIST OF ORIGINAL PUBLICATIONS

Publication I Leivo J, Anttonen E, Jolly SS, Džavík V, Koivumäki J, Tahvanainen M, Koivula K, Nikus K, Wang J, Cairns JA, Niemelä K, Eskola MJ. The high-risk ECG pattern of ST-elevation myocardial infarction: A substudy of the randomized trial of primary PCI with or without routine manual thrombectomy (TOTAL trial). Int J Cardiol. 2020 Nov 15;319:40-45. doi: 10.1016/j.ijcard.2020.05.053.

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AUTHOR'S CONTRIBUTION

In publications I, II and III, the author (J. Leivo) took part in the study design together with M. Eskola and K. Nikus, had a major role in data acquisition (ECG analysis), participated in conducting the statistical analyses together with J. Wang, as well as interpreted the results together with M. Eskola and K. Nikus and wrote and edited the manuscripts.

1 INTRODUCTION

Data from the World Health Organization (WHO) show that ischemic heart disease is the leading cause of death, accounting for 16% of deaths worldwide (World Health Organization 2020). In patients with an ST-elevation myocardial infarction (STEMI), there is wide variation concerning the individual risk of an adverse outcome. The current European Clinical Practice Guidelines (Byrne et al. 2023) recommend the use of the Global Registry of Acute Coronary Events (GRACE) risk score to assess the short-term and long-term outcome of STEMI patients (Fox et al. 2014). The GRACE risk score derives the risk estimation of an adverse outcome from several clinical factors and biomarkers, but they only include one crude ECG finding, ST deviation (Granger et al. 2003; Fox et al. 2006, 2014). A 12-lead ECG can be used for risk assessment in patients with a STEMI. It has been shown that the ECG findings contributing to the risk of an adverse outcome extend beyond ST segment deviation. The grade of ischemia (GI) ECG classification was developed by Sclarovsky and Birnbaum to assess the severity of ischemia and the risk of an adverse outcome. Along with changes in the ST segment, this classification is based on changes in the terminal portion of the QRS complex and in the T wave (Birnbaum et al. 1993). Another ECG classification based on changes in the Q wave, ST segment and T wave was developed by Sclarovsky in the late 1990s, signifying temporal changes in the course of a STEMI and consisting of two distinctive ECG patterns: preinfarction syndrome (PIS) and an evolving myocardial infarction (EMI) (Sclarovsky 1999).

Some early study data indicated that the use of thrombus aspiration during a primary percutaneous coronary intervention (pPCI) had the potential to improve the outcome of STEMI patients when compared to pPCI alone (Svilaas et al. 2008; Vlaar et al. 2008), and for many years, guidelines suggested the use of aspiration thrombectomy as an adjunctive treatment along with pPCI and to prevent the no-reflow phenomenon (Van de Werf et al. 2008). More recently, it was shown that routine aspiration thrombectomy yields no additional benefit in the treatment of STEMI patients, but the risk of stroke is increased in comparison to treatment with pPCI alone (Jolly et al. 2015). As a result, the routine use of aspiration thrombectomy

has been discarded in current guidelines, although it may still be considered in STEMI patients with a high thrombus burden (Ibanez et al. 2018; Neumann et al. 2019; Byrne et al. 2023). No previous studies have assessed the possible benefit of aspiration thrombectomy when STEMI patients are stratified into different risk groups according to their ECG findings.

The purpose of this dissertation was to assess the prognostic implications of different ECG classifications in STEMI patients, and whether any subgroup of STEMI patients, as stratified according to ECG findings, would benefit from aspiration thrombectomy.

2 REVIEW OF THE LITERATURE

2.1 ST-elevation myocardial infarction

2.1.1 Definition

Myocardial infarction (MI) is a consequence of myocardial cell death (necrosis) caused by prolonged myocardial ischemia. Moreover, myocardial ischemia is a consequence of imbalance between oxygen supply and demand. The classification of MI subtypes is based on pathological properties and the aetiology of the disease causing the MI. Type 1 MI is caused by underlying coronary artery disease (CAD), usually with a rupture or erosion of an atherosclerotic plaque forming a coronary thrombus that is seen in angiography. In addition to type 1 MI, there are four other types of MIs. Type 2 MI is defined as an imbalance between oxygen supply and demand unrelated to acute coronary thrombosis, causing myocardial ischemia. The potential aetiologic factors are severe anaemia or a coronary spasm. Type 3 MI comprises cardiac death as a result of acute ischemia, or a diagnosis of MI based on autopsy findings. Type 4 MI is related to a PCI procedure, while type 5 MI is defined as an MI related to a coronary artery bypass grafting (CABG) procedure. (Thygesen et al. 2018)

Acute coronary syndrome (ACS) is a broad term used for patients with acute myocardial ischemia, and it is classified into three different types: STEMI, non-ST-elevation MI (NSTEMI) and unstable angina pectoris (UAP) (Byrne et al. 2023). The initial diagnosis of ACS, STEMI or NSTEMI is made from the ECG with the important objective of selecting immediate reperfusion therapy for patients with a suspected ongoing acute coronary artery occlusion. In most cases, acute coronary artery occlusion results in ST elevation (STE), which is the hallmark diagnostic ECG finding of a STEMI. In an NSTEMI, the ECG often shows ST depression (STD) with or without T wave inversions (TWI), but the ECG can also be completely normal. Patients with UAP have intermittent symptoms of myocardial ischemia, the ECG findings are similar to those of an NSTEMI, but there is no elevation of cardiac troponin; therefore, UAP is regarded as myocardial ischemia without myocardial cell

death. (Ibanez et al. 2018; Thygesen et al. 2018; Collet et al. 2021; Byrne et al. 2023) There is no firm association between the different types of MI and ACS. Although STEMI patients typically have a type 1 MI, any other type of MI is also possible (Thygesen et al. 2018; Byrne et al. 2023).

2.1.2 Pathophysiology of STEMI

Multifactorial mechanisms are involved in the development of CAD. Known risk factors include elevated LDL cholesterol level, diabetes, hypertension, smoking and a family history of CAD (Bentzon et al. 2014). The involved pathophysiological mechanisms, including lipoprotein retention, inflammation, and smooth muscle cell proliferation, will eventually lead to the formation of atherosclerotic plaques. In the typical scenario, the onset of STEMI involves a sudden rupture or erosion of an atherosclerotic plaque, which leads to the formation of a luminal thrombosis or haemorrhage into the plaque. The thrombosis usually occludes the involved ('culprit') coronary artery completely, causing transmural ischemia in the affected myocardium, eventually leading to infarction if the artery remains occluded. Depending on prothrombotic and prothrombolytic factors, distal embolization into the artery may occur. Periodic spontaneous recanalization of the occlusion (spontaneous reperfusion) and pre-existing or developing collateral coronary artery flow protect the affected myocardium, thereby limiting the extent of the infarction. (Davies 2000; Falk et al. 2013; Bentzon et al. 2014)

2.1.3 Diagnosis of STEMI

2.1.3.1 Symptoms

Persistent chest pain is the typical presentation of myocardial ischemia. The pain can radiate to the neck, lower jaw or upper extremities. Upper gastrointestinal pain can also be a symptom of myocardial ischemia. Other atypical symptoms include fatigue, nausea, shortness of breath and palpitations; these symptoms are typically associated with older age. In some cases, myocardial ischemia and infarction may present without any symptoms, while cardiac arrest may be the only manifestation of an MI. (de Torbal et al. 2006; Ibanez et al. 2018; Thygesen et al. 2018; Byrne et al. 2023)

2.1.3.2 Electrocardiography

During the first medical contact, a 12-lead ECG should be recorded as quickly as possible in patients presenting with symptoms compatible with myocardial ischemia. Auxiliary leads for the diagnosis of right ventricular (V4R) (Lopez-Sendon et al. 1985) or inferolateral (formerly called posterior) (V7-9) (Matetzky et al. 1999; Birnbaum et al. 2022) STEMI may be used. For a STEMI diagnosis, a substantial STE must be present in two or more adjacent leads, and there should be no ECG findings of left ventricular hypertrophy (LVH) or bundle branch block. The STE is measured from the J point, using the TP or PR segment as a reference point (Figure 1). As for substantial STE, a cut-off point of 1 mm is used for all other leads except leads V2–3, V4R and V7–9. In leads V2 and V3, the cut-off point is as follows: ≥ 2 mm in men ≥ 40 years old, ≥ 2.5 mm in men < 40 years old, and ≥ 1.5 mm in women. For leads V4R and V7–9, the recommended cut-off point is ≥ 0.5 mm. (Thygesen et al. 2018)

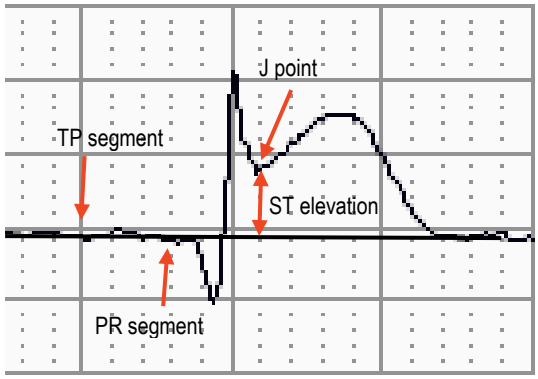


Figure 1. Representation of the TP segment, PR segment, J point, and measurement of ST elevation.

2.1.3.3 Cardiac troponin

As a result of myocardial injury, cardiac troponins I (TnI) and T (TnT) are released into the blood stream from myocardial cells, and high concentrations of these biomarkers are usually detected within a few hours after the onset of MI symptoms. (Keller et al. 2009; Mair et al. 2018). While the expression of TnI and TnT is almost exclusively confined to the myocardial cells, elevated TnT values are seen also in other types of muscle cell injury, not only in myocardial injury. Myocardial ischemia causes a myocardial injury, but the injury may also result from many other causes. (Thygesen et al. 2010, 2012, 2018; Jaffe et al. 2011; Rittoo et al. 2014) Myocardial ischemia which causes a rise or fall in cardiac troponin values when analysed sequentially, with at least one of the values above the 99th percentile of the upper reference limit, is defined as an acute MI (Thygesen et al. 2018). While the measurement of cardiac troponin has a central role making the final diagnosis of an MI, it is not required for the initial diagnosis of ACS and, for example, must not delay immediate reperfusion therapy for patients with a STEMI (Byrne et al. 2023).

2.1.3.4 Differential diagnostics

Minor STE in the precordial leads (V1–V6) is considered a normal finding in the general population and is more frequently seen in men than in women (Surawicz and Parikh 2002). In addition, ST elevation is more substantial in healthy individuals with the early repolarization pattern, where ST elevation is accompanied by a J wave (a positive notch or slur at the J point) (Kambara and Phillips 1976). Various conditions and diseases can also cause STEs resembling those encountered in STEMI. Classic examples of non-MI-related STEs include hyperkalaemia, Prinzmetal's angina (occlusive spasm of coronary artery) and perimyocarditis (Wang et al. 2003).

Cardiac troponin levels can be elevated due to illnesses not related to CAD, including myocarditis, sepsis/critical illness, acute or chronic kidney disease, heart failure (HF), takotsubo cardiomyopathy, stroke and pulmonary embolism (Kelley et al. 2009; Ilva et al. 2010; Agewall et al. 2011; Giannitsis and Katus 2013; deFilippi and Herzog 2017; Thygesen et al. 2018).

Furthermore, it may sometimes be difficult to rule out an MI with ECG and biomarkers alone. Various non-invasive imaging techniques can be used to differentiate an MI from other causes of chest pain or elevated troponin levels (Thygesen et al. 2018). Echocardiography is the most common imaging technique used in the setting of acute chest pain. It is helpful in, for example, assessing left

ventricular wall motion abnormalities related to myocardial ischemia. However, regional dysfunction of the ventricular wall can be seen both in acute myocardial ischemia and in post-MI scar regions. It should be noted that myocardial ischemia does not always cause infarction, and after successful reperfusion of the occluded coronary artery, wall motion abnormalities can resolve with time; one reason for this is myocardial stunning. (Sabia et al. 1991b, 1991a; Jeroudi et al. 1994; Thygesen et al. 2018) Cardiac magnetic resonance imaging (CMR), single-photon emission computed tomography (SPECT) and fluorodeoxyglucose positron emission tomography (FDG-PET) are not usually used in the acute setting of suspected myocardial ischemia. CMR is particularly helpful in assessing different types of myocardial injury (ischemic vs non-ischemic) – for instance, in the case of nonobstructive coronary arteries assessed by means of coronary angiogram. SPECT and FDG-PET can be used to evaluate myocardial perfusion and the viability of the myocardium in order to assess the feasibility of elective revascularisation therapy (usually PCI) with respect to patient outcome. (Thygesen et al. 2018; Mielniczuk et al. 2023)

2.1.3.5 Coronary thrombus in angiography

A coronary thrombus is generally defined as at least one of the following angiography findings: a hazy, spherical, ovoid, irregular or occlusive filling defect, an abrupt cutoff of the artery, and intraluminal staining (Zack et al. 1984; Capone et al. 1985; Dangas et al. 1997; Goldstein et al. 2000) (Figure 2). Ambrose et al. showed that eccentric or complex culprit artery lesions in angiography are often found in patients suffering an acute MI, and the authors suggested that this type of lesions were caused by plaque rupture or a coronary thrombus (Ambrose et al. 1985b, 1985a; Ambrose and Israel 1991). The complexity of culprit artery lesions was later found to correlate well with the presence of STEMI diagnosed by modern criteria (Ambrose et al. 2012). However, it was shown that the complex culprit lesion morphologies, as defined by Ambrose et al., do not correlate with the presence of a coronary thrombus (Amraotkar et al. 2017). The amount of thrombosis can be evaluated from angiography by comparing the dimensions of the thrombus with the dimensions of the normal coronary lumen. Based on this measurement, the thrombus burden is divided into different grades: grade 0, no thrombus; grade 1, possible thrombus; grade 2, small thrombus (greatest dimension less than ½ of the vessel diameter); grade 3, moderate thrombus (over ½ but less than 2 times the vessel diameter); grade 4, large thrombus (2 x the vessel diameter or more); and grade 5, total occlusion

(Gibson et al. 2001; Sianos et al. 2010). Furthermore, it was shown that a greater thrombus burden is associated with an adverse outcome in patients with an acute MI (The TIMI IIIA Investigators 1993; Zhao et al. 1999; Sianos et al. 2010). In addition to conventional angiography, intracoronary imaging (intravascular ultrasound, IVUS and optical coherence tomography, OCT) can be used to identify the presence of a coronary thrombus and to achieve a better assessment of lesion morphology (Johnson et al. 2019).

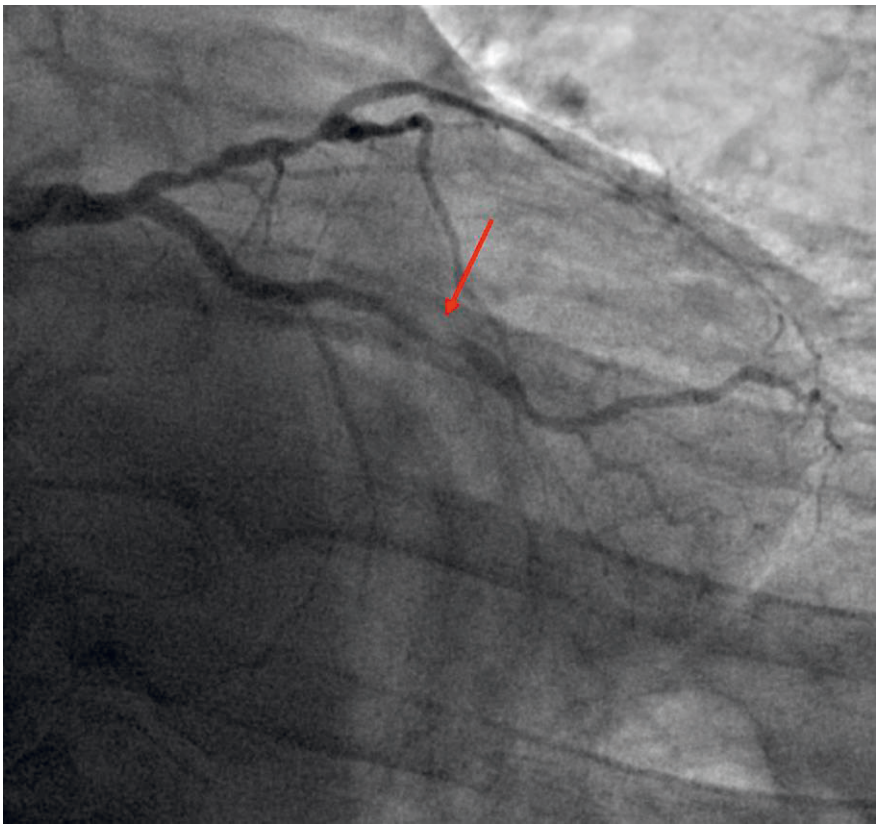


Figure 2. Coronary thrombus. Ovoid filling defect (red arrow) in the obtuse marginal branch of the LCx, marking a coronary thrombus (TIMI Thrombus grade 4).

2.1.4 Prognosis of STEMI

In the European countries, the annual incidence of STEMIs has been reported to range from 44 to 142 per 100,000 persons (Widimsky et al. 2010). Nikus et al. reported an in-hospital mortality rate of 9.6% in an unselected STEMI patient cohort (Nikus et al. 2007). However, the study was conducted in the pre-pPCI era, with 57% of the patients receiving fibrinolytic therapy (FT) upon hospital presentation. From the same cohort of STEMI patients, Konttila et al. reported the 10-year mortality to be as high as 52.5% (Konttila et al. 2021). Similarly, in a study from New Zealand, the in-hospital mortality rate of STEMI patients was 14%, rising to 58% during 13.5-year follow-up (Ellis et al. 2019); the rates of PCI and CABG during hospitalization were low (13% and 4%, respectively) (Ellis et al. 2004). In a study by Terkelsen et al., the total in-hospital and 1-year STEMI mortality rates were 10.9% and 20.5%, respectively, while the corresponding rates for patients receiving reperfusion therapy (pPCI or FT) were 4.9% and 10.5%, respectively (Terkelsen et al. 2005). Another study found that, in STEMI patients treated with pPCI or FT, the all-cause mortality rate was 27.3% with pPCI and 30.8% with FT during a median follow-up of 7.8 years (Nielsen et al. 2010). However, according to a study from Denmark, the cause of death after 30 days post-MI was usually noncardiac, with a < 1.5% annual risk of cardiac death (Pedersen et al. 2014).

To evaluate STEMI patients' risk of in-hospital and 6-month mortality, the Global Registry of Acute Coronary Events (GRACE) score was developed (Granger et al. 2003; Fox et al. 2006). The GRACE score includes the following parameters: age, heart rate, systolic blood pressure, creatine kinase (CK) level, Killip class, cardiac arrest at admission (yes/no), elevated cardiac biomarkers (yes/no), and ST segment deviation (STE or STD) (Granger et al. 2003). External validation of a data set containing patient data of 12,142 ACS patients showed excellent discriminatory capacity for both in-hospital (c-statistics 0.79) and 6-month (c-statistics 0.82) mortality, even when cardiac arrest could not be evaluated (Granger et al. 2003; Fox et al. 2006). Later on, the GRACE score has been validated for the assessment of the risk of 1- and 3-year mortality, and it has also been updated by substituting the CK level with a history of renal dysfunction and the Killip class with the use of diuretics (Fox et al. 2014). The current European guidelines for the management of ACS patients (Byrne et al. 2023) recommend the use of the GRACE score in risk assessment.

2.2 Dynamic ECG changes during STEMI

2.2.1 ST segment

At the onset of a coronary artery occlusion, a tall, positive and peaked T wave is the first sign of ongoing ischemia (Dressler and Roesler 1947; Nable and Brady 2009; Nikus et al. 2010). If the occlusion persists, the T wave alteration is quickly followed by STE. Acute transmural myocardial ischemia causes differences in electric currents between the ischemic and the non-ischemic myocardium, generating an 'injury current' from the ischemic region towards the normal cells. This appears as STE in the ECG leads facing the ischemic region. However, in a minority of cases, despite a total or near-total occlusion of the culprit artery, transmural ischemia does not develop, mainly due to collateral coronary artery flow, and a positive T wave might be the only ECG sing of ongoing ischemia. (Wagner et al. 1988; Berry et al. 1989; Sagie et al. 1989; Sclarovsky 1999; Nable and Brady 2009; Nikus et al. 2010)

Reciprocal STD is usually seen in the ECG leads, more or less anatomically opposite to the ones with STE. For example, in an anterior STEMI, STE in leads I and aVL is usually accompanied by STD in the inferior leads II, III and aVF. In contrast, STD in the anterior leads might be misdiagnosed as an NSTEMI in the case of an inferolateral STEMI, while STE is present only in leads V7–V9. (Sclarovsky et al. 1987; Agarwal et al. 1999; Sclarovsky 1999; Birnbaum and Drew 2003; Nikus et al. 2010; Birnbaum et al. 2022)

After reperfusion, spontaneous or therapy-induced, a resolution of STE is usually seen. The ST resolution is sometimes accompanied by negative T waves. In patients who are asymptomatic at presentation but report recent, fluctuating symptoms of myocardial ischemia, isolated TWI in the precordial leads represents critical left anterior descending coronary artery (LAD) occlusion with spontaneous reperfusion (Wellens' syndrome) (Figure 3). These patients are typically diagnosed to have NSTEMI, although, from a pathophysiological point of view, they have an anterior STEMI with spontaneous reperfusion (which explains the absence of symptoms). Studies performed before the reperfusion treatment era showed that a re-occlusion of the culprit artery occurred in the majority of cases, resulting in ECG findings of a STEMI. (de Zwaan et al. 1982, 1989; Sclarovsky 1999; Nikus et al. 2010)

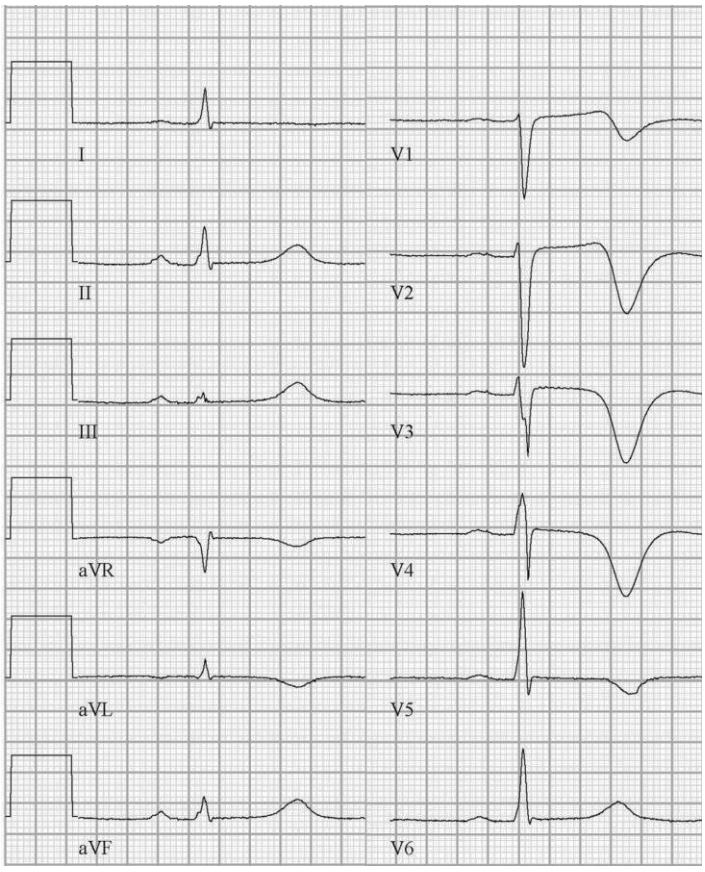


Figure 3. Wellens' syndrome. TWI is present in the precordial leads (and lead aVL) without significant STE or STD. Angiography revealed 90% stenosis of the LAD. Figure provided by Kjell Nikus.

2.2.2 T wave

The T wave reflects the electric repolarisation of myocytes (Yan and Antzelevitch 1998). In healthy adults, the T wave is normally negative in lead aVR and often also in leads III and V1 (Rautaharju et al. 2009; Aro et al. 2012). Investigators have used different cut-off values for a negative T wave. In the Fourth Universal Definition of Myocardial Infarction, a cut-off of 1 mm is used (Thygesen et al. 2018). It is also well known that a biphasic T wave may be an ECG sign of ACS – for example, in a minority of patients with Wellens' syndrome (type B) (de Zwaan et al. 1982; Byrne et al. 2023). Varying cardiac and non-cardiac diseases can cause TWI, but, importantly, without concomitant STE or STD, it is not a marker of ongoing ischemia. In the early phase of a STEMI, the T wave is positive in the leads with STE but can invert during the evolution of myocardial ischemia. (Hayden et al. 2002; de Luna et al. 2014; Said et al. 2015)

The mechanisms of TWI in the ECG of STEMI patients have not been fully explored and are possibly multifactorial. TWI in the presenting ECG of STEMI patients has been linked to the patency of the infarct-related artery (IRA) due to spontaneous reperfusion, but also to non-patency with no signs of reperfusion. Even after reperfusion therapy, TWI is not a reliable indicator of the patency of the IRA. Other explanations for the presence of TWI before reperfusion could be myocardial stunning or oedema, which has been the case in patients with an NSTEMI or myocarditis. (Matetzky et al. 1994; Herz et al. 1999; Wong et al. 1999; Sgarbossa et al. 2000; Pierard and Lancellotti 2005; Shimada et al. 2013; Alsaab et al. 2014; de Luna et al. 2014; Hira et al. 2014; De Lazzari et al. 2016; Cardona et al. 2018)

2.2.3 Q waves

Current guidelines define pathological Q waves as follows: any Q wave of > 20 ms in duration or a QS complex in leads V2 and V3; a Q wave of ≥ 30 ms in duration and ≥ 1 mm in depth in two or more adjacent leads. Q waves in leads III and V1 are not considered. Regarding leads V1 and V2, an R wave of > 40 ms in duration with an R/S ratio of > 1 and with a concomitant positive T wave is considered to be a pathological Q wave equivalent of the inferolateral wall. (Thygesen et al. 2018)

Generally, pathological Q waves have been regarded as a pathognomonic finding of myocardial necrosis. However, pathological Q waves can be seen in various cardiac diseases, including myocarditis, cardiac amyloidosis and hypertrophic cardiomyopathy. (Horan et al. 1971; Konno et al. 2004; Thygesen et al. 2018) In a

study by Raitt et al., Q waves in the presenting ECG of patients with an acute MI was a common finding, and the prevalence of Q waves did not increase even in patients with a longer time from symptom onset, as one could expect if Q waves were merely an indication of necrosis (Raitt et al. 1995). Pathological Q waves during ongoing ischemia may represent delayed intraventricular conduction. Moreover, pathological Q waves could be an indication of microvascular obstruction (MVO) or intramyocardial haemorrhage (IMH), as well as myocardial stunning. (Bateman et al. 1983; Selvester et al. 1988; Keeble et al. 2000; Tiller et al. 2019a)

2.2.4 Preinfarction syndrome and evolving MI

To distinguish between different temporal stages of a STEMI, the evolution of the ECG in connection with a STEMI was categorized into two distinct patterns by Sclarovsky: preinfarction syndrome (PIS) and evolving MI (EMI) (Figure 4).

The PIS pattern signifies an earlier stage of STEMI, as defined by substantial STE without pathological Q waves or TWI.

EMI represents a later stage of the disease process, and the EMI pattern can be further divided into three different subclasses, which are regarded as representations of different degrees of reperfusion. Firstly, Q waves might develop along with substantial STE and positive a T wave, signifying EMI without reperfusion. Secondly, while the ST segment remains elevated with or without Q waves, the T wave becomes inverted (being either biphasic with only a negative terminal portion or fully negative), indicating some degree of reperfusion (EMI with incomplete reperfusion). Lastly, fully inverted T waves, where ST segment resolution occurs with or without pathological Q waves, is considered to be EMI with complete reperfusion. (Sclarovsky 1999)

Considering the fact that ongoing myocardial ischemia is a dynamic process with the possibility of spontaneous reperfusion and re-occlusion, as well as the dependence of multiple other factors, PIS and the different EMI patterns might not always appear in a strict temporal order.

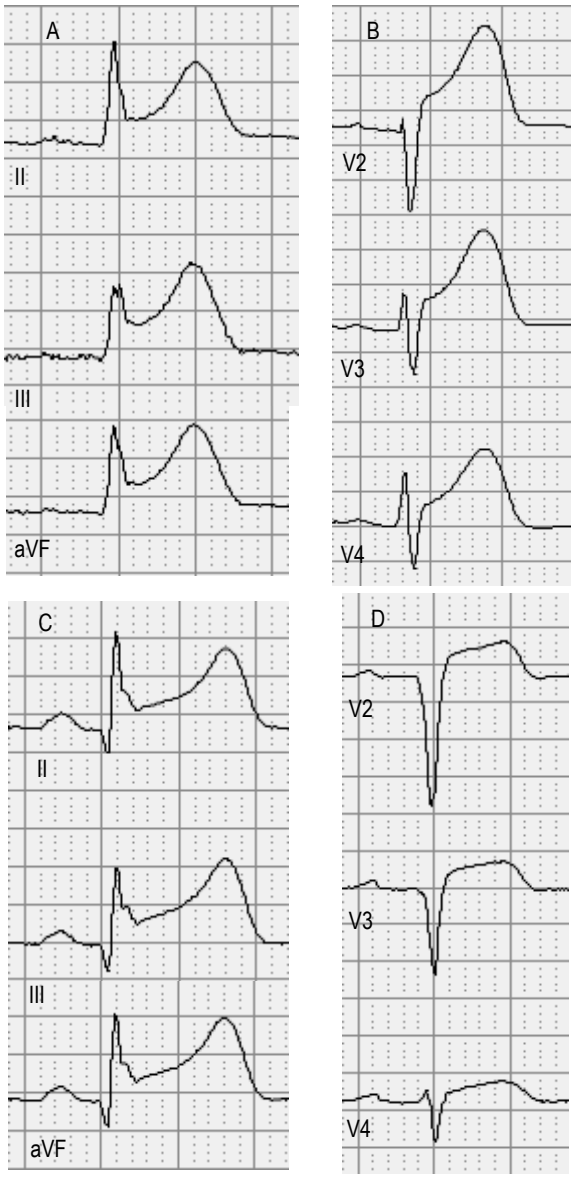


Figure 4. The PIS and EMI ECG patterns. STE without Q waves or TWI (PIS) in the inferior leads (A) and anterior leads (B). STE with Q waves (EMI) in the inferior leads (C) and anterior leads (D).

2.2.5 Grade of ischemia

Changes in the terminal portion of the QRS complex during acute myocardial ischemia were first described by Barnhill et al. (Barnhill et al. 1989). In the early 1990s, Sclarovsky and Birnbaum developed an ECG-based classification for risk stratification in patients with an acute MI (Sclarovsky et al. 1990). This classification signifies the severity of ischemia and is based on changes in the terminal portion of the QRS complex, the ST segment and the T wave. The first indication of acute myocardial ischemia is a tall, positive T wave indicating grade 1 ischemia (G1I). STE associated with a concomitant positive T wave and without changes in the QRS complex indicates grade 2 ischemia (G2I). If an elevated ST segment with a positive T wave is accompanied by a distortion of the terminal portion of the QRS complex, grade 3 ischemia (G3I) is present. The QRS distortion is demonstrated in rS-type complexes by the disappearance of the S wave, and in qR-type complexes by STE (J point amplitude) of ≥ 50 % of the height of the R wave. These changes in the terminal QRS must be present in at least two adjacent leads to be considered significant. (Birnbaum et al. 1993, 1996a) A presentation of G2I and G3I is shown in Figure 5.

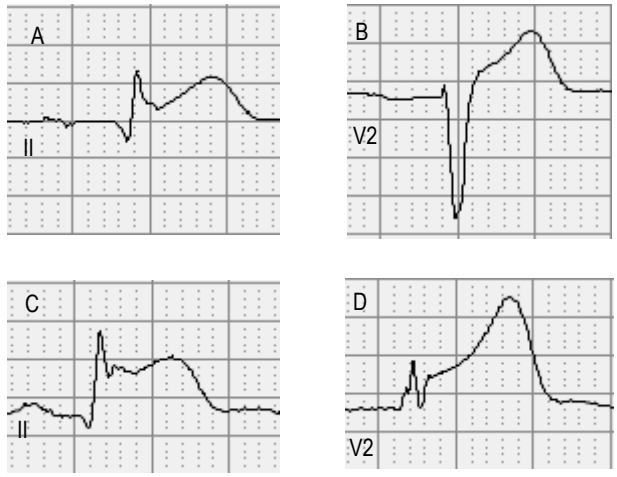


Figure 5. Grade of ischemia (GI). G2I in a qR-type complex (A) and in an rS-type complex (B). G3I in a qR-type complex (C) and in an rS-type complex (D).

The mechanism contributing to the distortion of the terminal QRS is not well understood. In the animal model, terminal QRS distortion may occur in the case of ischemia affecting the Purkinje fibre system, causing alterations in the depolarization velocity. Furthermore, since the Purkinje fibres are less sensitive to the effects of ischemia than is the myocardium, it is thought that this type of ischemia must be severe. In addition, it was suggested that the absence of ischemic preconditioning and poor collateral coronary artery flow might contribute to the occurrence of terminal QRS distortion. (Dehaan 1961; Holland and Brooks 1976; Birnbaum et al. 1993; Celik et al. 2008; Garcia-Rubira et al. 2008)

2.3 ECG-based risk stratification in STEMI

2.3.1 Infarct localization

The location of an MI is defined by the distribution of STE in the different contiguous lead groups: V1–V6 (anterior wall); II, III and aVF (inferior wall); I, aVL and V5–V6 (lateral wall); V7–V9 (inferolateral wall; previously described as posterior); and V4R (right ventricle). Accordingly, leads V5 and V6 may be regarded as anterior or lateral, depending on the distribution of ECG changes in the other leads (Lopez-Sendon et al. 1985; Matetzky et al. 1999; Zimetbaum and Josephson 2003; Thygesen et al. 2018). Studies have shown that patients with an anterior MI have a worse prognosis than patients with a non-anterior MI, regardless of the selected reperfusion strategy (pPCI vs FT). The difference in outcome has been thought to be largely explained by the size of the infarction (Geltman et al. 1979; Stone et al. 1988; Kandzari et al. 2006). Previously, the size of the infarction was estimated based on the degree of elevation in cardiac enzyme levels, especially serum CK, and the infarct size (IS) was shown to be an independent predictor of an adverse outcome in patients with an acute MI (Sobel et al. 1972; Geltman 1984). The relation between elevated CK or troponin levels and IS has been confirmed by modern-day CMR studies (Tiller et al. 2019b; Zhao et al. 2023). Moreover, imaging studies with SPECT and CMR have shown that a larger IS is associated with an elevated risk of cardiovascular (CV) death, re-infarction and new-onset heart failure (HF) (Miller et al. 1995; Eitel et al. 2014). However, results from CMR studies indicate that MVO is an even more significant factor predicting outcome than IS alone (Eitel et al. 2014; van Kranenburg et al. 2014).

2.3.2 Q waves

Pathological Q waves in the presenting ECG of STEMI patients have proved to be an independent predictor of an adverse outcome. Patients with Q waves had a roughly two-fold risk of cardiac death from the initial hospitalization for up to three years of follow-up compared to patients without Q waves. A higher risk of new or worsening HF and of cardiogenic shock was also associated with pathological Q waves. The effect of pathological Q waves on the outcome persisted regardless of the MI location (anterior vs non-anterior), the time from symptom onset to diagnosis or therapy, or the reperfusion strategy (pPCI vs FT). (Birnbaum et al. 1997; Wong et al. 2006; Eskola et al. 2007; Armstrong et al. 2009; Bao et al. 2014; Kosmidou et al. 2017; Zheng et al. 2017) Q waves were a predictor of a larger IS, lower EF, larger MVO and IMH as detected with CMR (Moon et al. 2004; Delewi et al. 2013; Topal et al. 2017; Tiller et al. 2019a). Furthermore, MVO and IMH have been linked to a poorer outcome in patients with a STEMI (Eitel et al. 2014; van Kranenburg et al. 2014; Reinstadler et al. 2019). STEMI patients with Q waves in the presenting ECG less frequently had TIMI grade-3 flow of the IRA (graded from 0 to 3, 0 indicating no flow and 3 indicating normal flow [TIMI Study Group 1985]) and ST resolution (STR) in the ECG after FT, indicating reduced reperfusion success. Lower rates of STR have also been observed in patients with Q waves treated with pPCI, even when the IRA was patent (TIMI 2–3 flow) after FT. (Wong et al. 1999, 2002; Zheng et al. 2017) It has been shown that, even though patients with Q waves have less myocardial salvage shortly after reperfusion by pPCI, myocardial salvage was still > 50% at 3 months' follow-up, indicating a benefit from reperfusion therapy (Topal et al. 2017).

In addition, Q waves may be transient, and the regression of Q waves after reperfusion therapy has been found in as many as 40% of patients with initial Q waves (Delewi et al. 2013). The regression of Q waves has been linked to smaller IS and better EF improvement, while the latter may be explained by a reduction of the IS itself as well as by a reversal of myocardial stunning. Despite these findings, Q wave regression was not independently associated with outcome. (Bateman et al. 1983; Barold et al. 1987; Coll et al. 1988; Lancellotti et al. 2002; Delewi et al. 2013; de Framond et al. 2019)

2.3.3 T wave inversions

STEMI patients with TWI in the initial ECG have been found to have a higher risk of in-hospital mortality, at least among patients presenting more than two hours after symptom onset (Herz et al. 1999). In addition, TWI was an independent predictor of a composite endpoint of death, re-infarction, cardiogenic shock, HF and target-vessel revascularisation as well as incomplete STR after reperfusion therapy during hospitalisation (Shimada et al. 2013). However, a recent study showed no independent effect of TWI on the 1-year mortality (Koivula et al. 2019). New TWIs can develop after reperfusion therapy, representing a potential indicator of a better in-hospital and long-term prognosis, as was shown with both FT and pPCI (Matetzky et al. 1994; Sgarbossa et al. 2000; Lee et al. 2017). In contrast, patients who had initial TWI persisting at four months had a worse 5-year outcome compared to patients with TWI normalisation. The adverse cardiac events evaluated in that study included cardiac death and a non-fatal MI (Lancellotti et al. 2002). Another study evaluated the correlation between persistent TWI and CMR findings, and persistent TWI at four months was a predictor of MVO and larger IS detected by CMR. However, TWI was assessed only from an ECG taken at four months, with no assessment of possibly existing TWI in the initial ECG. (Reindl et al. 2017)

2.3.4 Preinfarction syndrome and evolving MI

A study done by Eskola et al. was the first to evaluate the effect of the PIS and EMI ECG patterns on the outcome in patients treated with FT or pPCI. It was shown that the EMI pattern in the initial ECG was an independent predictor of a composite endpoint of death, re-infarction and stroke during 2.7-year follow-up. There was no difference between the two reperfusion treatments in outcome in the EMI group, but patients with anterior EMI without reperfusion (presence of Q waves without TWI) had a better prognosis when treated with pPCI. PIS patients also had a better outcome when treated with pPCI compared to FT. The effects of pathological Q waves and TWI were not evaluated separately in the study, but there was no difference in the outcome between EMI patients with (76% of the EMI patients) and those without pathological Q waves. (Eskola et al. 2007) Recently, Koivula et al. studied the effects of Q waves and TWI on the outcome of STEMI patients. Patients with both Q waves and TWI in the presenting ECG (EMI with incomplete reperfusion pattern) had a higher risk of 1-year mortality compared to patients without Q waves and TWI at presentation (PIS pattern). However, the ECG patterns

of Q waves or TWI alone were not independently predictive of an adverse outcome (Koivula et al. 2019).

2.3.5 Grade of ischemia

STEMI patients with G3I in the initial ECG had higher in-hospital mortality rates compared to patients with G2I, regardless of the selected reperfusion treatment. Birnbaum et al. first reported an in-hospital mortality rate of 29% in patients with G3I, while later studies have reported rates ranging from 6.8% to 17%. Patients with G3I also had a higher mortality during up to three years of follow up. (Birnbaum et al. 1993, 1996a, 1996b, 2001; Sejersten et al. 2006; Rommel et al. 2016; Koivula et al. 2018; Yılmaz et al. 2019) Some studies have suggested that the higher risk of an adverse outcome in G3I is confined to patients with an anterior MI or those treated two to three hours after symptom onset. However, G3I was an independent predictor of outcome regardless of the location of the MI or time delays. (Birnbaum et al. 1996b, 1996a; Sejersten et al. 2006) G3I has been linked to impaired STR, a higher rate of re-infarction, larger IS and reduced myocardial salvage when patients were treated with either FT or pPCI (Birnbaum et al. 1998, 2001, 2002; Lee et al. 2001; Billgren et al. 2005; Buber et al. 2005; Yang et al. 2005; McGehee et al. 2007; Weaver et al. 2011; Ringborn et al. 2014; Hassell et al. 2016; Rommel et al. 2016). Moreover, patients with G3I had larger MVO and IMH as assessed by CMR than did patients with G2I (Weaver et al. 2011; Rommel et al. 2016).

2.4 Reperfusion strategies in STEMI

2.4.1 The importance of time delays

It is well understood, and stated in the current guidelines, that reperfusion treatment should be performed on patients with a STEMI as expeditiously as possible (Ibanez et al. 2018; Neumann et al. 2019; Byrne et al. 2023). Numerous studies have shown that a longer delay before pPCI or FT increases the risk of in-hospital and overall mortality at least for up to 5.2 years of follow-up (Fibrinolytic Therapy Trialists' (FTT) Collaborative Group 1994; Cannon et al. 2000; Antoniucci et al. 2002; De Luca et al. 2003, 2004; Brodie et al. 2006; Terkelsen et al. 2010; Song et al. 2016). However, some studies have found a longer time to treatment to be an independent

predictor of an adverse outcome, while some have not (Cannon et al. 2000; Antoniucci et al. 2002; De Luca et al. 2003, 2004; Brodie et al. 2006; Terkelsen et al. 2010; Song et al. 2016). The results of previous studies are also inconsistent regarding possible differences between the time from symptom onset to reperfusion therapy and the time from hospital arrival to reperfusion therapy with respect to patient outcome (Cannon et al. 2000; De Luca et al. 2003; Brodie et al. 2006). Regarding different reperfusion treatment options and time delays, it has been proposed that the benefit of pPCI over FT in terms of outcome might be abolished if the time from hospital arrival to treatment is increased by more than one hour (Nallamothu and Bates 2003). However, STEMI patients treated with pPCI had lower mortality during 30-day follow-up compared to patients treated with FT, irrespective of treatment delays (Boersma and Primary Coronary Angioplasty vs. Thrombolysis Group 2006).

2.4.2 Fibrinolytic therapy

Intracoronary fibrinolysis was introduced as the first non-surgical method for reperfusion of an occluded coronary artery (Rentrop et al. 1980; Ganz et al. 1981). Studies with rather small numbers of patients suggested that patients receiving intracoronary fibrinolysis had lower in-hospital (5.4% vs 24%) and 3-month (6% vs 14%, $p = 0.006$) mortality when compared to patients who did not receive reperfusion therapy (Merx et al. 1981; Vermeer et al. 1986). Moreover, in-hospital systemic intravenous FT was found to be effective in restoring coronary blood flow (Schröder et al. 1983), but the reduction in mortality during three months of follow-up was not statistically significant (mortality 5.1% with FT vs 7.9% with placebo; rate ratio 0.64; 95% CI 0.37–1.13) (Van de Werf and Arnold 1988). FT administered in the pre-hospital setting during an acute MI shortens the time to effective reperfusion and has been proven safe, with a reduction in mortality and IS (Castaigne et al. 1987; McNeill et al. 1989; Barbash et al. 1990; Boersma et al. 1996; Morrison et al. 2000).

2.4.3 Primary percutaneous coronary intervention

A pPCI is regarded as the gold standard of reperfusion treatment in STEMI (Ibanez et al. 2018; Neumann et al. 2019). Some studies have shown a benefit of pPCI over FT regarding an adverse outcome among STEMI patients, while some have not. The

benefit of pPCI was suggested to be in relation to the baseline risk, the time of symptom onset and the delay in treatment. Furthermore, it was shown that the superiority of pPCI over FT remained if the delay of reperfusion therapy in patients treated with pPCI was no longer than 120 minutes. (Bonnefoy et al. 2002, 2009; Andersen et al. 2003; Keeley et al. 2003; Widimský et al. 2003; Betriu and Masotti 2005; Tarantini et al. 2005; Kent et al. 2007; De Luca et al. 2009; Terkelsen et al. 2009) However, Boersma et al. showed that pPCI was superior to FT regardless of the treatment delay (Boersma and Primary Coronary Angioplasty vs. Thrombolysis Group 2006). To establish a timely and most complete reperfusion in patients with a STEMI, studies were conducted to test the effectiveness and safety of facilitated PCI, where patients were given FT in conjunction with pPCI (Herrmann et al. 2000; Ellis et al. 2008). However, in a meta-analysis, facilitated PCI was not superior to pPCI alone (mortality rate 5% vs 3%; odds ratio [OR] 1.38; 95% CI 1.01–1.87; $p = 0.04$), while major bleeding (7% vs 5%; OR 1.51; 95% CI 1.10–2.08; $p = 0.01$) and haemorrhagic stroke (1.1% vs 0.3%; $p<0.001$) were found more frequently in patients undergoing combination therapy (Keeley et al. 2006).

The current guidelines recommend pPCI as the treatment of choice in patients with a STEMI, if the PCI can be performed within 120 minutes from the initial diagnosis. If the delay to PCI is presumed to be longer than 120 minutes, FT is preferred, and the recommendation is to administer the drug within 10 minutes from the decision on treatment strategy. STEMI patients who receive FT should be immediately transported to a PCI-capable hospital, and a rescue PCI should be performed if there is failed reperfusion (ECG finding of STR less than 50% within 90 minutes after FT) with FT. (Byrne et al. 2023)

2.5 Thrombus aspiration in STEMI

2.5.1 Thrombectomy procedure

Distal embolization of the occluded coronary artery can occur during STEMI, and this may result in less effective myocardial microcirculatory reperfusion even after successful reperfusion of the epicardial coronary artery by means of pPCI. The degree of myocardial perfusion can be assessed from the angiography with the aid of the myocardial blush grade. Furthermore, both distal embolization and reduced

myocardial perfusion are linked to higher mortality. (van 't Hof et al. 1998; Henriques et al. 2002; Stone et al. 2002; De Luca et al. 2005; Brener et al. 2011)

In order to minimize the risk of distal embolization and to improve myocardial reperfusion, different types of thrombectomy procedures have been evaluated for use in STEMI treatment with pPCI. There are three basic types of thrombectomy devices: manual, mechanical and vacuum (De Luca et al. 2006a; Tamhane et al. 2010). During manual aspiration thrombectomy, a thrombectomy device is inserted into the coronary artery after wire crossing of the culprit lesion. The device is first positioned proximally to the lesion, and aspiration is started before advancing the catheter over the lesion. Generally, multiple passings are required. After thrombectomy, the device is removed and the guiding catheter is aspirated for any residual clots or air. (Jolly et al. 2014) An example of aspiration thrombectomy is shown in Figure 6.

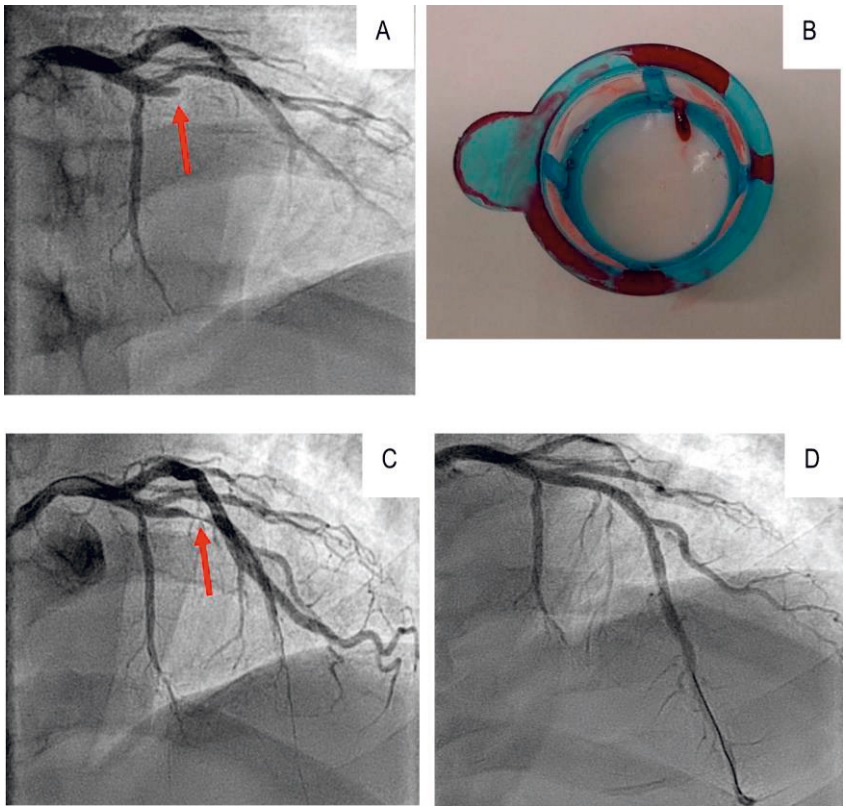


Figure 6. Manual aspiration thrombectomy. Panel A: Abrupt cutoff (red arrow) of the LAD as a sign of a thrombus (TIMI thrombus grade 5). Panel B: Thrombus aspirated from the coronary artery. Panel C: After thrombectomy, a significant narrowing (red arrow) of the LAD is seen. Panel D: The result after stenting. Figures provided by Markku Eskola.

2.5.2 Evidence of the benefit of thrombectomy

The results from numerous studies with rather small numbers of patients showed that treatment with thrombectomy resulted in better myocardial perfusion as assessed by the myocardial blush grade, and in reduced distal embolization and better STR when compared to treatment with pPCI alone (Beran et al. 2002; Napodano et al. 2003; Burzotta et al. 2005; Lefèvre et al. 2005; De Luca et al. 2006b; Silva-Orrego et al. 2006; Chevalier et al. 2008; Ikari et al. 2008; Svilaas et al. 2008; Sardella et al. 2009). One study, however, suggested that thrombectomy did not increase myocardial salvage and could be harmful because of an increase in IS (Kaltoft et al. 2006). The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) concluded that STEMI patients treated with manual aspiration thrombectomy had better myocardial reperfusion, defined as a lower rate of myocardial blush grade of 0 and 1 (graded from 0 to 3, 0 meaning no myocardial blush and 3 meaning normal myocardial blush [van 't Hof et al. 1998]; 17.1% in the thrombectomy group vs 26.3% in the PCI alone group; risk ratio 0.65; 95% CI 0.51–0.83; $p < 0.001$), and more complete STR (56.6% vs. 44.2%; risk ratio 1.28; 95% CI, 1.13–1.45; $p<0.001$) when compared to patients treated with pPCI alone (Svilaas et al. 2008). A follow-up study of the original TAPAS trial showed that patients in the pPCI alone group had higher 1-year cardiac mortality compared to patients in the thrombectomy group (6.7% vs 3.6%; hazard ratio [HR] 1.93; 95% CI 1.11–3.37; $p = 0.020$) (Vlaar et al. 2008). The guidelines for the treatment of STEMI patients published the same year suggested that manual aspiration thrombectomy could be used as adjunctive therapy to pPCI and to prevent the no-reflow phenomenon (Van de Werf et al. 2008).

However, a later meta-analysis concluded that there was no clear benefit from thrombectomy regarding 30-day mortality compared to pPCI alone (OR 0.84; 95% CI 0.54–1.29; $p = 0.42$), while there was a trend towards lower 30-day mortality with manual aspiration thrombectomy (OR 0.59; 95% CI 0.35–1.01; $p = 0.05$) and a trend towards higher 30-day mortality with mechanical devices (OR 2.07; 95% CI 0.95–4.48; $p = 0.07$) (Tamhane et al. 2010). The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial with over 7,200 patients showed that routine aspiration thrombectomy did not reduce the risk of 30-day all-cause mortality compared to pPCI alone (2.8% vs 3.0%; HR 0.94; 95% CI 0.72–1.22; $p = 0.63$) or the rate of stroke (0.5% vs 0.5%; OR 1.06; 95% CI 0.55–2.02; $p = 0.87$) (Fröbert et al. 2013).

Inspired by the inconsistency of the earlier results, the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) was conducted (Jolly et al. 2014). It is the largest trial to date regarding the use of routine aspiration thrombectomy in the treatment of STEMI patients, and it included 10,732 patients globally. It was shown that thrombectomy did not reduce the risk of cardiogenic shock, recurrent MI, HF or CV death during up to one year of follow-up (8% in the thrombectomy group vs 8% in PCI alone group; HR 1.00; 95% CI 0.87–1.15; p = 0.99). Neither did all-cause mortality differ between the thrombectomy and pPCI alone groups (4.3% vs 4.5%; HR 0.95; 95% CI 0.79–1.15; p = 0.60). Moreover, as an important safety factor, it was found that the risk of stroke was higher in patients treated with thrombectomy (1.2% vs 0.7%; HR 1.66; 95% CI, 1.10–2.51; p = 0.015). It was concluded by the authors that the routine use of thrombectomy along with pPCI should not be recommended. (Jolly et al. 2015, 2016)

There are no previous studies assessing the effect of aspiration thrombectomy on the outcome of patients with STEMI when patients are stratified into different risk groups based on the ECG findings.

2.5.3 Recent recommendations for the use of thrombectomy

The current guidelines for selecting the revascularization strategy in patients with STEMI do not recommend the routine use of thrombectomy. However, in patients with a high thrombus burden, thrombectomy may be used, at least in a trial setting, to discover a possibly beneficial effect. (Ibanez et al. 2018; Neumann et al. 2019; Byrne et al. 2023) In fact, a small pilot study is currently ongoing to determine the effectiveness and safety of stent retriever thrombectomy compared to aspiration thrombectomy and PCI alone when treating patients with a STEMI (Kotronias et al. 2023).

3 AIMS OF THE STUDY

The aim of this dissertation was to evaluate the prognostic significance of different dynamic ECG changes in STEMI patients treated with pPCI, and to assess whether any subgroup of STEMI patients, categorized according to the ECG changes, would benefit from routine aspiration thrombectomy.

The detailed aims were:

1. To assess the prognostic significance of the EMI and PIS ECG patterns, their correlation to angiographic data, and whether patients with the EMI or PIS ECG patterns would benefit from routine thrombectomy. (Study I)

2. To determine the prognostic impact of the GI ECG classification, its correlation to the angiographic data and whether patients with different GIs would benefit from routine thrombectomy. (Study II)

3. To evaluate the prognostic relevance of Q waves and TWI combined and separately, and whether patients with different combinations of Q waves and TWI would benefit from routine thrombectomy. (Study III)

4 MATERIALS AND METHODS

4.1 Patients

The TOTAL trial was an international, multicentre, randomized study, which enrolled 10,732 patients from August 2010 to July 2014. Patients had symptoms of myocardial ischemia and an ECG indicating STEMI, and they were referred to pPCI within 12 hours of symptom onset and randomly assigned to receive either aspiration thrombectomy with PCI or PCI without thrombectomy. A 12-lead ECG was taken before and 30–60 minutes after the index treatment assignment from all patients. All patients enrolled in the study provided written informed consent. (Jolly et al. 2015) All of the ECG substudies of the TOTAL trial presented in this thesis were pre-planned (Jolly et al. 2014).

All patients in the TOTAL trial who had undergone the index treatment and had a baseline ECG available (n = 10,064), were screened for inclusion in Studies I, II and III. Patients were excluded based on the following ECG findings: left bundle branch block (n = 62), other broad QRS >120 ms (n = 486), poor ECG quality (n = 703) and ECG criteria of STEMI unfulfilled (n = 953). In addition, patients with TWI were excluded from Study II (n = 649) because GI cannot be analysed in the presence of TWI, and, due to the nature of the study, patients with missing data on Q waves or TWI were excluded from Study III (n = 29).

4.1.1 Study I

Patients (n = 7,860) were divided into two groups based on the ECG findings of EMI and PIS. The EMI group consisted of 2,618 patients and the PIS group of 5,242 patients.

4.1.2 Study II

Patients (n = 7,211) were divided into two groups based on the GI ECG classification: G3I (n = 1,563) and G2I (n = 5,648).

4.1.3 Study III

Patients (n = 7 831) were divided into four groups based on the presence of Q waves and TWI in the pre-procedure ECG, as shown in Figure 7. The Q-TWI- (no Q wave and no TWI) group consisted of 5,242 patients, the Q+TWI- (Q wave present but no TWI) group of 1,922 patients, the Q-TWI+ (no Q wave but TWI present) group of 354 patients and the Q+TWI+ (both Q wave and TWI present) group of 313 patients. In addition, patients were divided into four groups according to Q waves and TWI independently of one another: Q waves present and Q waves not present (n = 2,235 and n = 5,596, respectively) and TWI present and TWI not present (n = 667 and n = 7,164, respectively).

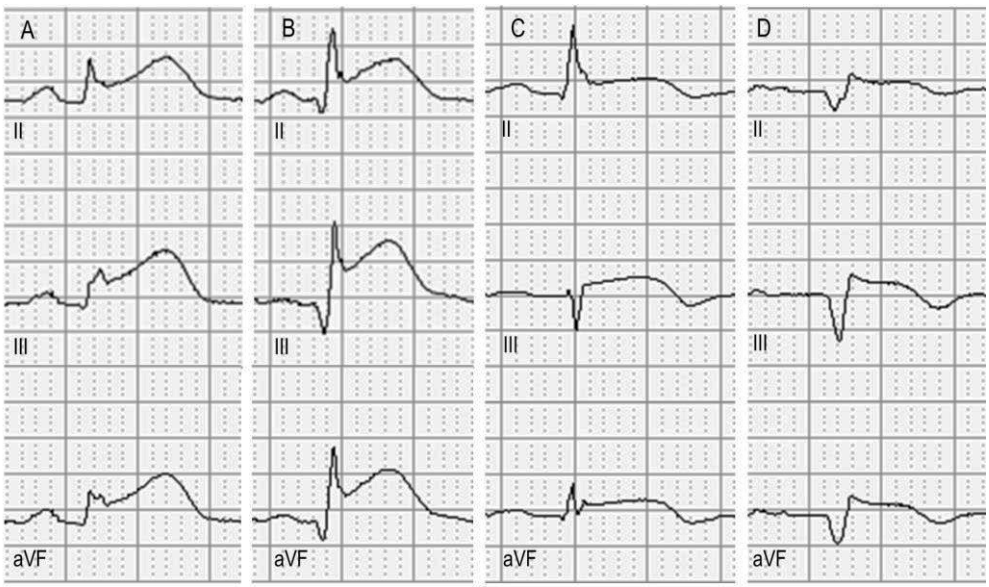


Figure 7. Different Q wave and TWI groups in the inferior leads. A: Q-TWI- (no Q wave and no TWI); B: Q+TWI- (Q wave but no TWI); C: Q-TWI+ (no Q wave but TWI); D: Q+TWI+ (both Q wave and TWI).

4.2 ECG analyses

All of the ECG analyses for the TOTAL trial were conducted in the Heart Hospital, Tampere University Hospital, by the investigators of the ECG core laboratory. Measurements were taken manually from the baseline ECG and recorded before the index treatment, and investigators were blinded to the clinical and angiographic data as well as to the treatment assignment.

4.2.1 ST elevation

STE was measured from the J point, while the TP segment was regarded as the isoelectric line. Contrary to the current STEMI guidelines (Thygesen et al. 2018), a modified cut-off point of 2 mm was used for leads V2 and V3 because the investigators were blinded to the patients' age and sex. For all other leads, a cut-off point of 1 mm was applied.

4.2.2 Location of the MI

The location of the STEMI was based on the maximal STE in the different lead groups. If maximal STE was detected in leads V1–V6, the STEMI was regarded as anterior, while maximal STE in leads II, III and aVF was regarded as inferior and in leads I, aVL, V5 and V6 as lateral.

4.2.3 Q waves

Q waves in leads V2 and V3 were regarded as pathological if a QS complex was present or the duration of the Q wave was ≥ 20 ms, regardless of the Q wave amplitude. For all other leads, pathological Q waves were defined as a Q wave of ≥ 30 ms in duration and ≥ 1 mm in amplitude, when present in two or more adjacent leads.

4.2.4 T waves

T waves were considered inverted if a fully negative or a biphasic T wave with a ≥ 0.5 mm negative terminal segment was present.

4.3 Outcomes

For studies I, II and III, the primary outcome measure was a composite of cardiovascular death, recurrent MI, new or worsening New York Heart Association (NYHA) class IV HF or cardiogenic shock during 1-year follow-up. Secondary outcomes were all-cause death (studies I, II and III), primary outcome plus stent thrombosis or target-vessel revascularisation (TVR; studies I and II), stroke (study I) and stroke or transient ischemic attack (TIA, study II) within one year.

4.4 Statistical analyses

Categorical variables were expressed as numbers and percentages and continuous variables as mean ± standard deviation (SD) or median with interquartile range (IQR). The Chi-squared test was used to assess differences between categorial variables. The two-sample t-test (studies I and II) or ANOVA test (study III) was used for normally distributed continuous variables, while the Wilcoxon rank-sum test (studies I and II) or Kruskal-Wallis test (study III) was used for non-normally distributed continuous variables. The effect of different ECG changes on the risk of primary and secondary outcomes was evaluated with the Cox regression model. HRs and 95% CIs were reported. Schoenfeld residuals were used to evaluate the proportional hazard assumption of the Cox regression model. In Study III, a violation of the proportional hazard assumption was detected, and an extended Cox regression model with a time-dependent covariate was therefore implemented. The optimal change point τ was identified with the τ value that maximized the log partial likelihood. Depending on joint or separate analysis of Q waves and TWI as well as clinical outcomes, the optimal change point ranged from 35 to 45 days. A change point of 40 days was selected for the analyses for the purposes of straightforward interpretation and presentation of the results.

Cumulative incidences of primary outcome and cardiovascular death (studies I and II) or all-cause death (study III) were charted by Kaplan-Meier curves. Multivariable analyses were performed by forcing age and symptom onset (6–12 hours vs < 6 hours) into the model. Sex, current smoking, hypertension, diabetes mellitus, location of MI, previous MI, proximal lesion, previous PCI, heart rate, Killip class ≥ 2, TIMI 0 flow before PCI, thrombus grade (5 vs < 5), time from symptom onset to procedure (per 10 minutes increment), elevated troponin and cardiogenic shock (Studies I, II and III), along with the presence of pathological Q waves, systolic blood pressure, creatinine and cardiac arrest (Study II), were tested for incorporation based on their confounding effects and overall model fit. To achieve parsimonious models, a backwards elimination approach was used to exclude variables with p value > 0.05. Apart from achieving a parsimonious multivariable model, Study II included another multivariable analysis, where all of the above-mentioned variables were included in the multivariable model. Propensity score matching was applied as a sensitivity analysis in Studies I and II, where all of the aforementioned variables respective to the multivariable models in the studies were included in the propensity score model. EMI and PIS patients were matched in a 1:1 ratio (Study I), and G3I and G2I patients in a 1:3 ratio (Study II), with calliper width set at 0.2 of pooled SD of logit of propensity score (Austin 2011) in both studies. Matching quality was assessed with standardized difference, and a value of < 0.1 was considered negligible, while the difference between the respective groups were assessed with Cox regression with robust standard errors (Studies I and II). The consistency with which the EMI and PIS ECG patterns affected the risk of primary outcome in the prespecified subgroups was assessed in Study I. The differences were examined by the likelihood ratio test of the interaction term in an unadjusted Cox regression model and presented as a forest plot.

The incremental prognostic value of EMI and PIS ECG patterns when combined with the GRACE score was evaluated in Study I. Two multivariable Cox regression models where constructed, one with components of the GRACE score (age, heart rate, Killip class, creatinine, cardiac arrest and elevated troponin) and another including EMI and PIS ECG patterns combined with components of the GRACE score. The comparison of these two models were carried out using the likelihood ratio test. Discriminatory capacity was evaluated with C-statistics, and the reclassification capacity of added ECG pattern was assessed with the continuous Net Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI) (Pencina et al. 2011). A two-tailed p value of < 0.05 was considered statistically

significant for all analyses. All analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

4.5 Ethical aspects

All patients who gave written informed consent for the TOTAL trial consented to being included in the pre-planned substudies of the trial, including the ECG substudies. All study data were stored and maintained by the Population Health Research Institute in Hamilton, Canada (the principal unit of the TOTAL trial). The patients enrolled in the trial were given a study participant code, without any of the investigators having knowledge of the patients' identity. The ECG substudies utilized the data collected for the main trial, and no additional data were collected from the patients' medical records. All collected data were treated confidentially, and patients had the right to discontinue their participation in the trial at any time. The Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital had approved the TOTAL trial to be conducted in part at the Heart Hospital, Tampere University Hospital, before the start of patient enrolment.

5 SUMMARY OF THE RESULTS

5.1 Prognostic significance of EMI and PIS ECG changes (Study I)

Of the 7,860 patients, 2,618 (33%) had the EMI pattern and 5,242 (67%) the PIS pattern present in their ECG. There were some differences between the two groups regarding clinical and procedural characteristics, as shown in Table 1. The patients with EMI were more often male, their Killip class was more often ≥ 2, and their time from symptom onset to hospital arrival and onwards to the PCI procedure was longer. They also more often had elevated troponin levels at admission, TIMI 0 flow before PCI and an anterior MI, when compared to patients with PIS. There were no differences between the two groups regarding medical history.

At the 1-year follow-up mark, the primary outcome had occurred in 271 (10.4%) patients in the EMI group and 322 (6.1%) patients in the PIS group (HR, 1.73; 95% CI 1.47–2.03; $p < 0.001$) (Figure 8). When the components of the primary outcome were analysed separately, the patients with EMI had a higher rate of CV deaths, cardiogenic shock and NYHA class IV HF, but there was no difference in the incidence of recurrent MI between the groups. The rates of all-cause mortality and stent thrombosis were also higher in the EMI group. In the multivariable analysis, the ECG pattern of EMI vs PIS remained independently predictive of the primary outcome (adjusted HR, 1.54; 95% CI 1.30–1.82; $p< 0.001$). Other variables that were independently predictive included age, female sex , diabetes, previous MI, proximal lesion, heart rate, Killip class ≥2, thrombus grade (5 vs < 5), and cardiogenic shock. In contrast, symptom onset (6–12 h vs < 6 h) was not independently predictive. The results are shown in Table 2. The effect of the ECG changes on the primary outcome within one year did not differ between the preselected subgroups (Figure 9).

Table 1. Clinical and procedural characteristics according to EMI and PIS (Study I).

Characteristics[a]	EMI, n = 2618	PIS, n = 5242	p value
Age (years)	60.8 ± 12.0	60.6 ± 11.8	0.465
Male sex	2092 (79.9)	3985 (76.0)	< 0.001
Heart rate (bpm)	80.1 ± 17.8	74.3 ± 16.9	< 0.001
Systolic blood pressure (mmHg)	136.7 ± 26.2	134.7 ± 26.5	0.001
Diastolic blood pressure (mmHg)	84.2 ± 16.6	81.7 ± 16.4	< 0.001
BMI (kg/m^2)	27.2 ± 4.5	27.8 ± 4.7	< 0.001
Killip class ≥ 2	142 (5.4)	164 (3.1)	< 0.001
Location of MI			< 0.001
Anterior	1580 (60.4)	1480 (28.2)	
Inferior	944 (36.1)	3494 (66.7)	
Lateral or other	92 (3.5)	265 (5.1)	
Elevated troponin at admission	1771 (67.6)	2833 (54.0)	< 0.001
Medical history			
Previous stroke	72 (2.8)	155 (3.0)	0.606
Hypertension	1280 (48.9)	2604 (49.7)	0.513
Diabetes	449 (17.2)	944 (18.0)	0.348
Previous MI	250 (9.5)	433 (8.3)	0.056
Previous PCI	213 (8.1)	423 (8.1)	0.919
Peripheral arterial disease	61 (2.3)	108 (2.1)	0.437
Current smoker	1195 (45.6)	2408 (45.9)	0.807
Time to initial PCI procedure			
Symptom onset to hospital arrival (min)	142.0 (82.0–252.0)	114.0 (66.0–190.0)	< 0.001
Hospital to initial PCI procedure (min)	55.0 (25.0–90.0)	48.0 (21.0–85.0)	< 0.001
TIMI thrombus grade[b]			0.052
0: no thrombus	62 (2.4)	135 (2.6)	
1: possible thrombus	108 (4.1)	278 (5.3)	
2: definitive thrombus, < 0.5 x vessel diameter	64 (2.4)	153 (2.9)	
3: definitive thrombus, 0.5–2.0 x vessel diameter	267 (10.2)	556 (10.6)	
4: definitive thrombus, > 2.0 x vessel diameter	330 (12.6)	727 (13.9)	
5: total occlusion	1786 (68.2)	3390 (64.7)	
TIMI 0 flow before PCI[C]	1847 (70.6)	3462 (66.0)	< 0.001

EMI, evolving myocardial infarction; PIS, preinfarction syndrome; bpm, beats per minute; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

[a]Values are given as number and percentage, mean ± SD, or median and interquartile range.

[b]The thrombus grade is measured as the largest dimension of the thrombus as compared with the diameter of the vessel in which it occurs.

[C]TIMI flow graded on a scale of 0 to 3, with a higher grade indicating better flow.

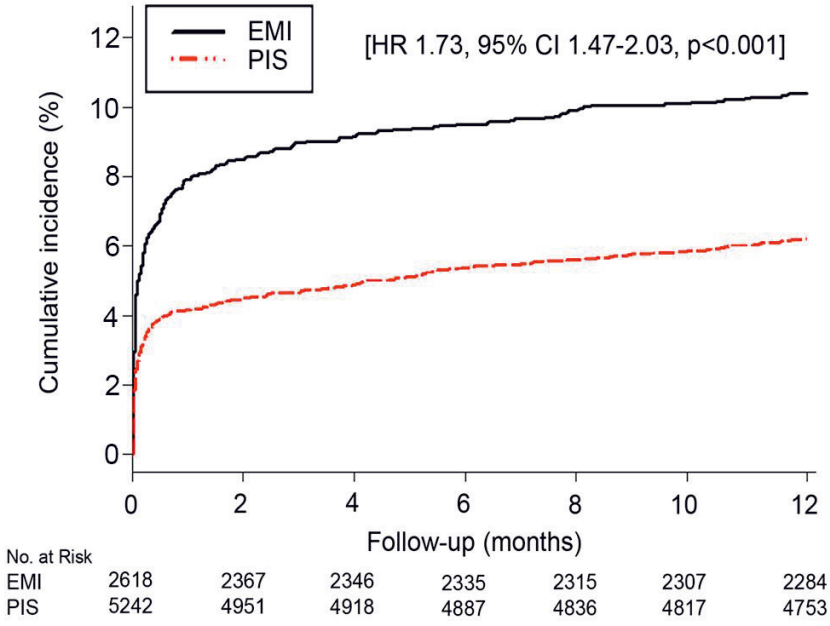


Figure 8. Kaplan-Meier estimates of the primary outcome (Study I). The risk of a composite of CV death, recurrent MI, cardiogenic shock, or NYHA class IV heart failure within one year in patients with EMI and PIS ECG patterns.

Table 2. Primary and secondary outcomes, and multivariable analysis of primary outcome (Study I).

Univariable analysis	EMI (n = 2618)	PIS (n = 5242)	HR (95% CI)[a]	p value
Primary outcome	271 (10.4%)	322 (6.1%)	1.73 (1.47–2.03)	< 0.001
Cardiovascular death	131 (5.0%)	127 (2.4%)	2.10 (1.64–2.68)	< 0.001
Recurrent MI	73 (2.8%)	124 (2.4%)	1.20 (0.90–1.60)	0.223
Cardiogenic shock	75 (2.9%)	69 (1.3%)	2.21 (1.59–3.06)	< 0.001
Class IV heart failure	73 (2.8%)	75 (1.4%)	1.99 (1.44–2.74)	< 0.001
Primary outcome plus stent thrombosis or TVR	358 (13.7%)	505 (9.6%)	1.46 (1.27–1.67)	< 0.001
All-cause mortality	149 (5.7%)	166 (3.2%)	1.83 (1.46–2.28)	< 0.001
Stent thrombosis	66 (2.5%)	95 (1.8%)	1.41 (1.03–1.93)	0.032
TVR	143 (5.5%)	277 (5.3%)	1.05 (0.86–1.29)	0.634
Stroke	25 (1.0%)	44 (0.8%)	1.16 (0.71–1.89)	0.559

Multivariable analysis	aHR (95% CI)	p value
EMI vs PIS ECG pattern	1.54 (1.30–1.82)	<0.001
Age (per 10-year increment)	1.51 (1.41–1.63)	<0.001
Symptom onset (6–12 h vs < 6 h)	1.12 (0.91–1.38)	0.302
Sex (female)	1.38 (1.16–1.66)	<0.001
Diabetes	1.67 (1.39–2.01)	<0.001
Previous MI	1.61 (1.27–2.04)	<0.001
Proximal lesion	1.22 (1.03–1.43)	0.020
Heart rate, per 10 bpm increment	1.16 (1.11–1.21)	<0.001
Killip class ≥ 2	1.78 (1.34–2.36)	<0.001
Thrombus grade (5 vs < 5)	1.19 (1.00–1.41)	0.050
Cardiogenic shock	3.41 (2.11–5.49)	<0.001

EMI, evolving myocardial infarction; PIS, preinfarction syndrome; TVR, target-vessel revascularisation; HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio.

[a] HR and 95% CI calculated using an unadjusted Cox regression model.

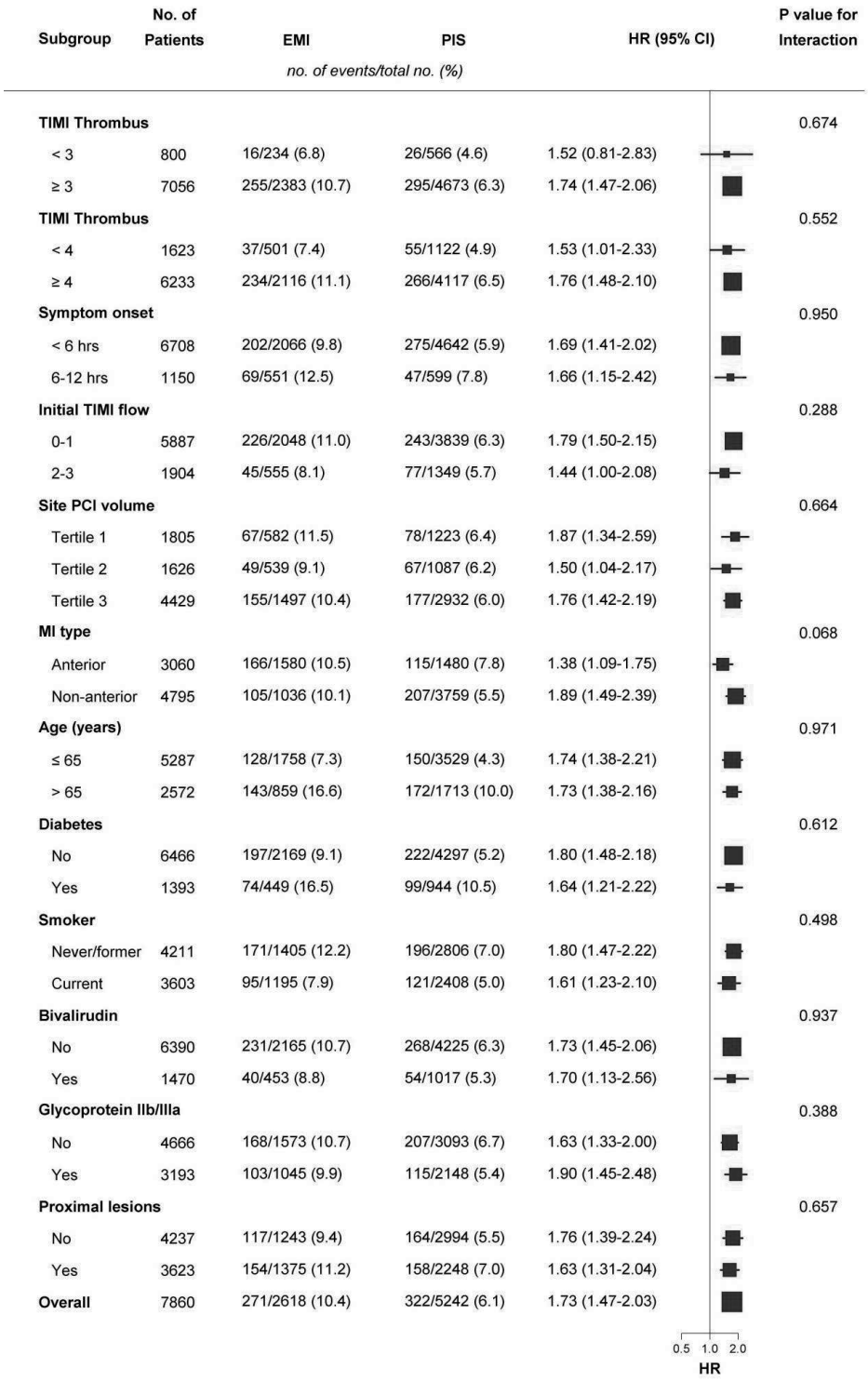


Figure 9. Forest plot (Study I). The effects of EMI and PIS ECG changes on the risk of primary outcome within one year in prespecified subgroups.

In the propensity score analysis, 1,848 EMI patients were matched to 1,848 PIS patients, and selected variables displayed a good balance between the two patient groups (Table 3). The EMI patients had a higher risk of a primary outcome compared to the PIS patients (10.5% vs 7.5%; HR 1.43; 95 % CI 1.15–1.77; $p = 0.001$).

A significant incremental prognostic value of the EMI and PIS ECG patterns was detected after addition to the GRACE score by the likelihood ratio test ($p < 0.001$). This finding was supported by continuous NRI (0.279; 95% CI 0.192–0.368) and relative IDI (0.085; 95% CI 0.48–0.125). Furthermore, a modest increase in C-statistics was observed (0.712; 95% CI 0.688–0.735 [GRACE score alone] and 0.719; 95% CI 0.694–0.742 [GRACE score with EMI and PIS ECG patterns]; $p = 0.088$).

Table 3. Evaluation of balance of baseline covariates before and after 1:1 propensity score matching* (Study I)

	Pre-match			Post-match		
Characteristics[a]	EMI, n = 2618	PIS, n = 5242	Standardized difference†	EMI, n = 1848	PIS, n = 1848	Standardized difference†
Age (years)	60.8±12.0	60.6±11.8	0.0175	60.6±12.0	60.5±11.9	0.0081
Symptom onset (6-12hrs vs. <6hrs)	551 (21.0)	599 (11.4)	0.2632	328 (17.7)	307 (16.6)	0.0301
Sex (female)	526 (20.1)	1257 (24.0)	-0.0939	393 (21.3)	364 (19.7)	0.0389
MI type (non-anterior vs anterior)	1036 (39.6)	3759 (71.7)	-0.6839	860 (46.5)	865 (46.8)	-0.0054
Current smoking	1195 (45.6)	2408 (45.9)	-0.0045	851 (46.0)	853 (46.2)	-0.0022
Hypertension	1280 (48.9)	2604 (49.7)	-0.0160	924 (50.0)	944 (51.1)	-0.0216
Diabetes	449 (17.2)	944 (18.0)	-0.0226	329 (17.8)	319 (17.3)	0.0142
Previous MI	250 (9.5)	433 (8.3)	0.0452	169 (9.1)	179 (9.7)	-0.0185
Previous PCI	213 (8.1)	423 (8.1)	0.0024	158 (8.5)	158 (8.5)	0.0000
Proximal lesion	1375 (52.5)	2248 (42.9)	0.1938	898 (48.6)	873 (47.2)	0.0271
Heart rate (bpm)	80.1±17.8	74.3±16.9	0.3328	78.4±17.4	78.5±17.7	-0.0074
Killip class ≥ 2	142 (5.4)	164 (3.1)	0.1138	100 (5.4)	93 (5.0)	0.0170
Elevated troponin	1771 (67.6)	2833 (54.0)	0.3070	1417 (76.7)	1408 (76.2)	0.0115
TIMI 0 flow before PCI	1847 (70.6)	3461 (66.0)	0.0971	1261 (68.2)	1280 (69.3)	-0.0222
Thrombus grade (5 vs < 5)	1660 (63.4)	3101 (59.2)	0.0887	1136 (61.5)	1144 (61.9)	-0.0089
Time from symptom onset to procedure (min)	263.4±195	213.4±143	0.2928	245.2±155	241.8±160	0.0216
Cardiogenic shock	27 (1.0)	43 (0.8)	0.0221	18 (1.0)	19 (1.0)	-0.0054

EMI, evolving myocardial infarction; PIS, preinfarction syndrome; bpm, beats per minute; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

*Caliper width for propensity score matching was set at 0.2 of pooled standard deviation of the logit of propensity score. One EMI patient was matched to one PIS patient.

[a]Values are given as number and percentage or mean ± SD.

† A standardized difference of < 0.1 was considered as a negligible difference between groups.

5.2 Prognostic impact of the grade of ischemia (Study II)

The baseline data for patients with G3I (n = 1,563) and G2I (n = 5,648) are shown in detail in Table 4. In brief, patients with G3I were marginally older and more often had a diagnosis of hypertension, Killip class of ≥ 2, TIMI thrombus grade 5 and TIMI 0 flow before PCI, and their time from symptom onset to hospital arrival was marginally longer. Regarding ECG findings, the patients with G3I more frequently had inferior infarcts and pathological Q waves than patients with G2I.

Patients with G3I had a higher risk of the primary outcome compared to patients with G2I (9.8% vs 6.4%; aHR, 1.27; 95 % CI 1.04–1.55; p= 0.022). This was explained by a higher incidence of CV death and recurrent MI in the G3I group, while the difference between the two groups regarding NYHA class IV HF or cardiogenic shock was not statistically significant. Patients with G3I also had a higher rate of stent thrombosis, but no difference was detected regarding all-cause death, as shown in Table 5. Among patients with G3I, the other independent predictors of adverse outcome were age, female sex, anterior MI, diabetes, cardiogenic shock, previous MI, elevated heart rate, Killip class ≥ 2, elevated creatinine, cardiac arrest and pathological Q waves. Systolic blood pressure (per 10 mmHg increment) was also an independent predictor but was negatively associated with the primary outcome.

After 1:3 propensity score matching, all of the selected variables were equally distributed among 1,490 patients in the G3I group and 4,135 patients in the G2I group. Patients in the G3I group had a higher risk of the primary outcome and cardiovascular death compared to the G2I group (9.33% vs 7.4%; HR 1.28; 95% CI 1.05–1.56; p = 0.016; and 4.36% vs 2.81%; HR 1.57; 95% CI 1.17–2.11; p = 0.003, respectively), but there was no difference in the incidence of recurrent MI, cardiogenic shock or HF between the two patient groups.

Table 4. Baseline data of patients according to the grade of ischemia (Study II).

Variables[a]	G3I (n = 1563)	G2I (n = 5648)	p value
Age, years	61.5 ± 11.6	60.3 ± 11.8	< 0.001
Sex (male)	1222 (78.2)	4383 (77.6)	0.626
Heart rate (beats per minute)	77.7 ± 17.6	75.4 ± 17.1	< 0.001
Systolic blood pressure (mmHg)	133.6 ± 26.3	135.7 ± 26.2	0.006
Diastolic blood pressure (mmHg)	82.3 ± 16.5	82.5 ± 16.4	0.787
Killip class ≥ 2	79 (5.1)	200 (3.5)	0.006
Q waves in baseline ECG	548 (35.1)	1403 (24.8)	< 0.001
Location of MI			< 0.001
Anterior	591 (37.8)	2138 (37.9)	
Inferior	929 (59.4)	3209 (56.8)	
Lateral or other	42 (2.7)	297 (5.3)	
Medical history			
Previous stroke	54 (3.5)	149 (2.6)	0.084
Hypertension	808 (51.7)	2745 (48.6)	0.030
Diabetes	262 (16.8)	984 (17.4)	0.542
Previous MI	136 (8.7)	492 (8.7)	0.990
Previous PCI	128 (8.2)	461 (8.2)	0.972
Peripheral arterial disease	40 (2.6)	111 (2.0)	0.147
Current smoker	712 (45.6)	2613 (46.3)	0.618
Elevated troponin	887 (56.7)	3246 (57.5)	0.610
Time to initial PCI procedure			
Onset to hospital (min)	123.0 (75.0–210.0)	119.0 (70.0–200.0)	0.008
Hospital to procedure (min)	50.0 (22.0–83.0)	49.0 (21.0–85.0)	0.843
Initial TIMI thrombus grade			0.003
0	29 (1.9)	143 (2.5)	
1	55 (3.5)	290 (5.1)	
2	34 (2.2)	157 (2.8)	
3	144 (9.2)	597 (10.6)	
4	195 (12.5)	754 (13.3)	
5	1106 (70.8)	3703 (65.6)	
TIMI 0 flow before PCI[b]	1149 (73.5)	3776 (66.9)	< 0.001

MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.
[a]Values are given as number and percentage, mean ± SD, or median and interquartile range.
[b]TIMI flow graded on a scale of 0–3, with a higher grade indicating better flow.

Table 5. Multivariable Cox regression model of the effect of grade of ischemia on the outcome (Study II).

Outcomes	Grade 3 (n=1563)	Grade 2 (n=5648)	aHR (95% CI)*	p value
Primary outcome	153 (9.8%)	364 (6.4%)	1.27 (1.04–1.55)	0.022
Cardiovascular death	75 (4.8%)	143 (2.5%)	1.48 (1.09–2.00)	0.013
Recurrent MI	52 (3.3%)	123 (2.2%)	1.54 (1.11–2.16)	0.013
Cardiogenic shock	38 (2.4%)	89 (1.6%)	1.14 (0.76–1.71)	0.544
Class IV heart failure	39 (2.5%)	92 (1.6%)	1.24 (0.84–1.84)	0.282
All-cause mortality	82 (5.2%)	186 (3.3%)	1.25 (0.94–1.65)	0.128
Stent thrombosis	52 (3.3%)	94 (1.7%)	1.85 (1.30–2.62)	< 0.001

MI, myocardial infarction.

* Adjusted for age, symptom onset (6–12 h vs < 6 h), sex, location of MI, current smoking, hypertension, diabetes, previous MI, previous PCI, proximal lesion, heart rate, Killip class ≥ 2, TIMI 0 flow before PCI, Thrombus grade (5 vs < 5), time from symptom onset to procedure (per 10 mins increment), prior cardiogenic shock, pathological Q waves, systolic BP, creatinine, and cardiac arrest.

5.3 Analysis of Q waves and TWI (Study III)

Of the 7,831 patients, 5,242 (67%) had the Q-TWI- ECG pattern, 1,922 (24.5%) the Q+TWI- pattern, 354 (4.5%) the Q-TWI+ pattern, and 313 (4%) the Q+TWI+ pattern. There was some heterogeneity among the four groups regarding baseline attributes, as shown in Table 6. In brief, an anterior location of the MI was more frequent in the Q+TWI- and Q+TWI+ groups. The Q+TWI+ group also more often had elevated troponin levels at admission and a longer time from symptom onset to the PCI procedure. TIMI thrombus grade 5 and TIMI 0 flow before PCI was more frequently seen in patients with the Q+TWI- pattern. A diagnosis of diabetes was more frequent in patients with the Q-TWI+ and the Q+TWI+ pattern, but the medical histories were otherwise similar among the groups.

In a multivariable analysis of different Q wave and TWI groups (Table 7), the risks of primary outcome and all-cause death in patients with the Q+TWI+ pattern were higher compared to patients with the Q-TWI- pattern within 40-day follow-up (10.5% vs 4.2 %; aHR 2.10; 95% CI 1.45–3.04; $p < 0.001$, and 7.0% vs 1.6%; aHR 3.50; 95% CI 2.17–5.65; $p < 0.001$, respectively), but after the 40-day mark, there was no additive risk of either primary outcome or all-cause death. Similarly, the risks of primary outcome and all-cause death were higher in patients with the Q+TWI- pattern than in those with the Q-TWI- pattern within 40 days but not beyond 40 days. In contrast, patients with the Q-TWI+ pattern had a higher risk of primary outcome only after 40 days (aHR 1.82; 95% CI 1.06–3.14; $p = 0.031$). There was a trend towards a difference in the risk of all-cause death between patients with the Q-TWI+ and those with the Q-TWI- pattern after 40 days, but the result was not statistically significant.

Cumulative incidences of the primary outcome and all-cause death within one year in the different Q wave and TWI groups are presented in Figure 10.

Table 6. Baseline attributes of different Q wave and TWI categories (Study III).

Attributes[a]	Q-TWI- (n=5242)	Q+TWI- (n=1922)	Q-TWI+ (n=354)	Q+TWI+ (n=313)	p value
Age (year)	60.6 ± 11.8	60.4 ± 11.6	63.2 ± 12.3	60.9 ± 13.0	< 0.001
Sex (Male)	3985 (76.0)	1576 (82.0)	240 (67.8)	253 (80.8)	< 0.001
Heart rate (beats per minute)	74.3 ± 16.9	80.1 ± 17.5	77.1 ± 19.2	83.6 ± 17.5	< 0.001
Systolic blood pressure	134.7 ± 26.5	136.5 ± 25.4	136.9 ± 28.7	138.5 ± 28.3	0.006
Diastolic blood pressure	81.7 ± 16.4	84.5 ± 16.5	81.9 ± 16.5	84.8 ± 17.4	< 0.001
BMI, kg/m^2	27.8 ± 4.7	27.3 ± 4.3	27.4 ± 4.9	26.7 ± 4.6	< 0.001
Killip class ≥ 2	164 (3.1)	109 (5.7)	12 (3.4)	19 (6.1)	< 0.001
Location of MI					< 0.001
Anterior	1480 (28.2)	1222 (63.6)	144 (40.7)	202 (64.5)	
Inferior	3494 (66.7)	626 (32.6)	201 (56.8)	101 (32.3)	
Lateral or other	265 (5.1)	72 (3.7)	9 (2.5)	10 (3.2)	
Hypertension	2604 (49.7)	924 (48.1)	193 (54.5)	149 (47.6)	0.131
Diabetes	944 (18.0)	296 (15.4)	78 (22.0)	70 (22.4)	< 0.001
Previous MI	433 (8.3)	185 (9.6)	29 (8.2)	31 (9.9)	0.258
Previous PCI	423 (8.1)	157 (8.2)	26 (7.3)	25 (8.0)	0.964
Peripheral arterial disease	108 (2.1)	41 (2.1)	10 (2.8)	10 (3.2)	0.461
Current smoker	2408 (45.9)	891 (46.4)	149 (42.1)	139 (44.4)	0.478
Elevated troponin	2833 (54.0)	1259 (65.5)	251 (70.9)	241 (77.0)	< 0.001
Symptom onset to hospital	114.0 (66.0–190.0)	136.0 (80.0–235.0)	162.0 (82.0–300.0)	185.0 (100.0–360.0)	< 0.001
Hospital to PCI procedure	48.0 (21.0–85.0)	50.0 (23.0–84.0)	65.0 (28.0–104.0)	67.0 (31.0–101.0)	< 0.001
TIMI thrombus grade 5	3390 (64.7)	1389 (72.3)	193 (54.5)	184 (58.8)	< 0.001
TIMI 0 flow before PCI	3462 (66.0)	1428 (74.3)	194 (54.8)	202 (64.5)	< 0.001

Abbreviations as in Table 1; [a] Values are given as number and percentage, mean ± SD, or median and interquartile range.

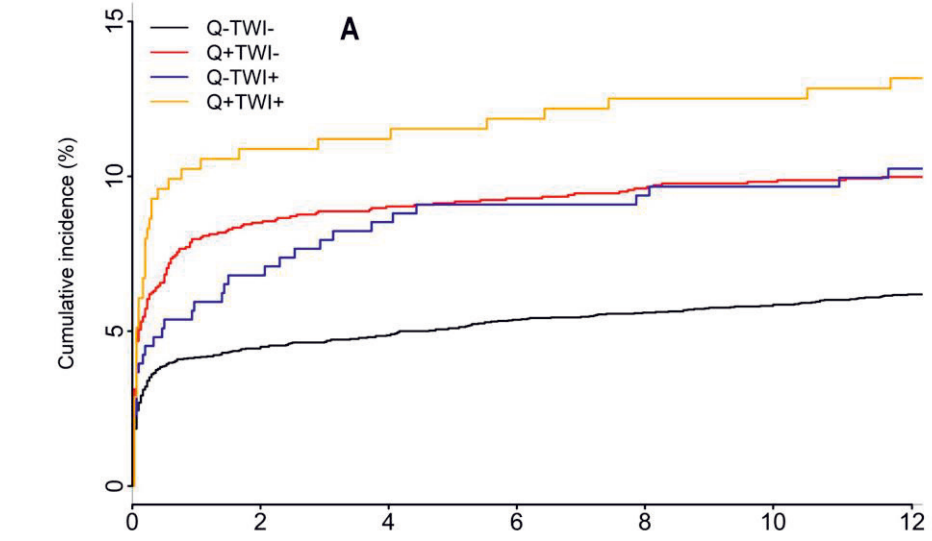
Table 7. Analysis of the effect of different Q wave and TWI categories on the primary outcome and all-cause death during time periods before and after 40 days (Study III).

	Period 1: ≤ 40 days			Period 2: > 40 days		
Primary outcome	n/N(%)	aHR (95% CI)[a]	p value	n/N(%)	aHR (95% CI)[a]	p value
Q-TWI-	221/5242 (4.2)	ref	-	101/4970 (2.0)	ref	-
Q+TWI-	157/1922 (8.2)	1.78 (1.44–2.20)	< 0.001	34/1746 (1.9)	0.96 (0.65–1.42)	0.838
Q-TWI+	21/354 (5.9)	1.08 (0.68–1.71)	0.743	15/329 (4.6)	1.82 (1.06–3.14)	0.031
Q+TWI+	33/313 (10.5)	2.10 (1.45–3.04)	< 0.001	8/277 (2.9)	1.28 (0.62–2.64)	0.504
All-cause death	n/N(%)	aHR (95% CI)[b]	p value	n/N(%)	aHR (95% CI)[b]	p value
Q-TWI-	83/5242 (1.6)	ref	-	83/5118 (1.6)	ref	-
Q+TWI-	71/1922 (3.7)	1.96 (1.42–2.72)	< 0.001	28/1838 (1.5)	0.85 (0.55–1.31)	0.455
Q-TWI+	11/354 (3.1)	1.47 (0.78–2.78)	0.230	12/340 (3.5)	1.65 (0.90–3.03)	0.106
Q+TWI+	22/313 (7.0)	3.50 (2.17–5.65)	< 0.001	4/290 (1.4)	0.64 (0.24–1.77)	0.393

aHR, adjusted hazard ratio; CI, confidence interval.

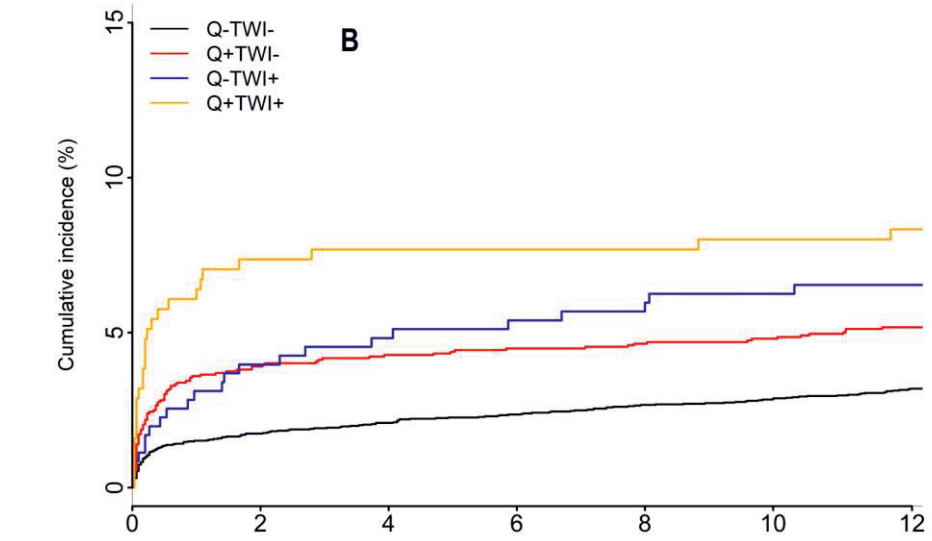
[a] Adjusted for age, symptom onset, sex, diabetes, previous MI, proximal lesion, heart rate, Killip class ≥ 2, cardiogenic shock

[b] Adjusted for age, symptom onset, diabetes, previous MI, previous PCI, proximal lesion, heart rate, Killip class of ≥ 2, cardiogenic shock



No. at Risk

Q-TWI-	5242	4951	4918	4887	4836	4817	4753
Q+TWI-	1922	1738	1726	1720	1708	1702	1687
Q-TWI+	354	326	320	317	314	313	308
Q+TWI+	313	275	273	271	268	267	265



No. at Risk

Q-TWI-	5242	5108	5089	5073	5036	5025	4968
Q+TWI-	1922	1834	1826	1822	1818	1813	1798
Q-TWI+	354	337	334	332	330	328	323
Q+TWI+	313	288	287	287	286	285	284

Figure 10. Kaplan-Meier estimates of the risk of primary outcome and all-cause death (Study III). Cumulative incidences of the primary outcome (composite of CV death, recurrent MI, cardiogenic shock, or NYHA class IV heart failure; panel A) and all-cause death (panel B) within one year in different Q wave and TWI categories.

The distribution of baseline variables among patients with and without Q waves is shown in Table 8 and among those with and without TWI in Table 9. Pathological Q waves in the baseline ECG increased the risk of the primary outcome only within 40 days (aHR, 1.80; 95% CI 1.48–2.19; $p < 0.001$) – the same was true for all-cause death. Regarding patients with TWI, the risk of the primary outcome was higher only after the 40-day point when compared to patients with no TWI in the baseline ECG (aHR, 1.63; 95% CI 1.04–2.55; $p = 0.033$). However, the risk of all-cause death was higher with TWI within 40 days (aHR, 1.65; 95% CI 1.13–2.41; $p = 0.010$), but not after 40 days. The results are presented in Table 10.

Table 8. Baseline variables for patients with and without Q waves (Study III).

Characteristics[a]	Q wave (n = 2235)	No Q wave (n = 5596)	p value[b]
Age (year)	60.5 ± 11.8	60.8 ± 11.8	0.326
Sex (Male)	1829 (81.8)	4225 (75.5)	< 0.001
Heart rate, beats per minute	80.6 ± 17.5	74.5 ± 17.1	< 0.001
Systolic BP (mmHg)	136.8 ± 25.8	134.8 ± 26.6	0.003
Diastolic BP (mmHg)	84.6 ± 16.6	81.7 ± 16.4	< 0.001
BMI (kg/m^2)	27.2 ± 4.4	27.8 ± 4.7	< 0.001
Killip class ≥ 2	128 (5.7)	176 (3.1)	< 0.001
Location of MI			< 0.001
Anterior	1424 (63.7)	1624 (29.0)	
Inferior	727 (32.5)	3695 (66.0)	
Lateral or other	82 (3.7)	274 (4.9)	
Hypertension	1073 (48.0)	2797 (50.0)	0.115
Diabetes	366 (16.4)	1022 (18.3)	0.048
Previous MI	216 (9.7)	462 (8.3)	0.045
Previous PCI	182 (8.1)	449 (8.0)	0.861
Peripheral arterial disease	51 (2.3)	118 (2.1)	0.634
Current smoker	1030 (46.1)	2557 (45.7)	0.753
Total CK (U/L)	306.0 (136.0–1095)	195.5 (106.0–538.0)	< 0.001
Elevated troponin	1500 (67.1)	3084 (55.1)	< 0.001
Initial PCI procedure			
Onset to hospital (min)	140.0 (81.0–250.0)	115.0 (68.0–195.0)	< 0.001
Hospital to procedure (min)	53.0 (23.0–87.0)	49.5 (22.0–86.0)	0.114
Initial TIMI thrombus grade			< 0.001
0	45 (2.0)	152 (2.7)	
1	83 (3.7)	302 (5.4)	
2	53 (2.4)	164 (2.9)	
3	214 (9.6)	603 (10.8)	
4	266 (11.9)	789 (14.1)	
5	1573 (70.4)	3583 (64.0)	
TIMI 0 flow before PCI	1630 (72.9)	3656 (65.3)	< 0.001
Concomitant medications			
Clopidogrel	1652 (73.9)	3884 (69.4)	< 0.001
Ticagrelor	488 (21.8)	1510 (27.0)	< 0.001
Oral anticoagulants	188 (8.4)	269 (4.8)	< 0.001

BP, blood pressure; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CK, creatine kinase; TIMI, Thrombolysis In Myocardial Infarction.

[a] Values are given as number and percentage, mean ± SD, or median and interquartile range.

[b] p value is from Chi-squared test for categorical variables and two-sample t-test for continuous variables.

Table 9. Baseline variables for patients with and without TWI (Study III).

Characteristics[a]	TWI (n = 667)	No TWI (n = 7164)	p value[b]
Age (year)	62.1 ± 12.7	60.5 ± 11.7	0.002
Sex (Male)	493 (73.9)	5561 (77.6)	0.029
Heart rate, beats per minute	80.1 ± 18.7	75.9 ± 17.3	< 0.001
Systolic BP (mmHg)	137.6 ± 28.5	135.2 ± 26.2	0.034
Diastolic BP (mmHg)	83.3 ± 17.0	82.4 ± 16.5	0.217
BMI (kg/m2)	27.1 ± 4.8	27.6 ± 4.6	0.003
Killip class ≥2	31 (4.6)	273 (3.8)	0.284
Location of MI			< 0.001
Anterior	346 (51.9)	2702 (37.7)	
Inferior	302 (45.3)	4120 (57.5)	
Lateral or other	19 (2.8)	337 (4.7)	
Hypertension	342 (51.3)	3528 (49.2)	0.316
Diabetes	148 (22.2)	1240 (17.3)	0.002
Previous MI	60 (9.0)	618 (8.6)	0.746
Previous PCI	51 (7.6)	580 (8.1)	0.683
Peripheral arterial disease	20 (3.0)	149 (2.1)	0.118
Current smoker	288 (43.2)	3299 (46.0)	0.155
Total CK (U/L)	460.5 (157.0–1211)	210.0 (111.0–626.0)	< 0.001
Elevated troponin	492 (73.8)	4092 (57.1)	< 0.001
Initial PCI procedure			
Onset to Hospital (min)	170.0 (88.0–335.0)	120.0 (70.0–200.0)	< 0.001
Hospital to procedure (min)	66.0 (30.0–103.0)	49.0 (22.0–85.0)	< 0.001
Initial TIMI thrombus grade			< 0.001
0	26 (3.9)	171 (2.4)	
1	40 (6.0)	345 (4.8)	
2	24 (3.6)	193 (2.7)	
3	82 (12.3)	735 (10.3)	
4	118 (17.7)	937 (13.1)	
5	377 (56.5)	4779 (66.7)	
TIMI 0 flow before PCI	396 (59.4)	4890 (68.3)	< 0.001
Concomitant medications			
Clopidogrel	488 (73.2)	5048 (70.5)	0.143
Ticagrelor	147 (22.0)	1851 (25.8)	0.031
Oral anticoagulants	42 (6.3)	415 (5.8)	0.595

Abbreviations as in Table 8.

[a] Values are given as number and percentage, mean ± SD, or median and interquartile range.

[b] p value is from Chi-squared test for categorical variables and two-sample t-test for continuous variables.

Table 10. Analysis of the effect of Q waves and TWI separately on the primary outcome and on all-cause death during time periods before and after 40 days (Study III).

	Period 1: ≤ 40 days			Period 2: > 40 days		
Primary outcome	n/N(%)	aHR (95% CI)[a]	p value	n/N(%)	aHR (95% CI)[a]	p value
No Q wave	242/5596 (4.3)	ref	-	116/5299 (2.2)	ref	-
Q wave	190/2235 (8.5)	1.80 (1.48–2.19)	< 0.001	42/2023 (2.1)	0.91 (0.63–1.30)	0.600
No TWI	378/7164 (5.3)	ref	-	135/6716 (2.0)	ref	-
TWI	54/667 (8.1)	1.14 (0.85–1.52)	0.392	23/606 (3.8)	1.63 (1.04–2.55)	0.033
All-cause death	n/N(%)	aHR (95% CI)[b]	p value	n/N(%)	aHR (95% CI)[b]	p value
No Q wave	94/5596 (1.7)	ref	-	95/5458 (1.7)	ref	-
Q wave	93/2235 (4.2)	2.01 (1.50–2.71)	< 0.001	32/2128 (1.5)	0.76 (0.50–1.14)	0.183
No TWI	154/7164 (2.1)	ref	-	111/6956 (1.6)	ref	-
TWI	33/667 (4.9)	1.65 (1.13–2.41)	0.010	16/630 (2.5)	1.31 (0.77–2.22)	0.323

aHR, adjusted hazard ratio; CI, confidence interval.

[a] Adjusted for age, symptom onset, sex, diabetes, previous MI, proximal lesion, heart rate, Killip class ≥ 2, cardiogenic shock

[b] Adjusted for age, symptom onset, diabetes, previous MI, previous PCI, proximal lesion, heart rate, Killip class ≥ 2, cardiogenic shock

5.4 The effect of treatments on the outcome (Studies I, II and III)

The effect of PCI with routine aspiration thrombectomy or of PCI alone on the primary outcome was similar between all patient groups stratified by ECG changes (Table 11). For patients with the Q+TWI+ pattern, there was a tendency towards a benefit from routine aspiration thrombectomy, but the result was not statistically significant (Study III). In Study I, the effects of the two treatments on the risk of primary outcome did not differ between the EMI and PIS patients. However, when components of the primary outcome were analysed separately, there was a tendency towards a benefit from thrombectomy regarding the risk of cardiogenic shock in PIS patients, but the result was not statistically significant (1.0% with thrombectomy vs 1.6% with PCI alone; HR 0.63; 95% CI 0.39–1.03).

Table 11. Effect of treatments on the primary outcome subgrouped by different ECG changes (Studies II and III).

	Thrombectomy		PCI alone			
ECG change	events/ patients	event rate (%)	events/ patients	event rate (%)	HR (95% CI)	p value for interaction[a]
Q-TWI-	162/2633	6.2	160/2609	6.1	1.00 (0.81–1.25)	0.451
Q+TWI-	97/964	10.1	94/958	9.8	1.03 (0.77–1.37)	
Q-TWI+	20/186	10.8	16/168	9.5	1.13 (0.58–2.18)	
Q+TWI+	14/142	9.9	27/171	15.8	0.60 (0.31–1.15)	
Q wave						
No	182/2819	6.5	176/2777	6.3	1.02 (0.83–1.25)	0.606
Yes	111/1106	10.0	121/1129	10.7	0.93 (0.72–1.21)	
TWI						
No	259/3597	7.2	254/3567	7.1	1.01 (0.85–1.20)	0.343
Yes	34/328	10.4	43/339	12.7	0.80 (0.51–1.26)	
GI						
G2I	178/2832	6.3	186/2816	6.6	0.95 (0.77–1.17)	0.496
G3I	80/786	10.2	73/777	9.4	1.08 (0.79–1.49)	

TWI, T wave inversion; GI, grade of ischemia; HR, hazard ratio; CI, confidence interval.

[a] p value for interaction is from a likelihood ratio test of interaction term, using an unadjusted Cox regression model.

6 DISCUSSION

6.1 Main findings of the study

STEMI patients with pathological Q waves and/or TWI in the presenting ECG had a higher risk of an adverse outcome compared to patients without Q waves or TWI (Study I). This finding is in accordance with previous studies (Eskola et al. 2007; Koivula et al. 2019). Also, in line with previous studies, a higher risk of an adverse outcome was seen in patients with G3I as opposed to G2I in the presenting ECG (Study II). While patients with both pathological Q waves and TWI in the presenting ECG had the highest risk of an adverse outcome, Q waves and TWI affected the outcome in different temporal stages post-PCI. The effect of Q waves on the outcome seemed to apply only in the early stages after PCI, while TWI only affected the outcome later (Study III). Routine aspiration thrombectomy did not reduce the risk of an adverse outcome even in high-risk subgroups of patients as stratified by ECG changes (Studies I, II and III).

6.2 Risk stratification

6.2.1 GRACE score and ECG parameters

The GRACE score has been well validated in different patient populations to assess the risk of an adverse outcome in ACS. The score includes several clinical factors and biomarkers, yet only one ECG parameter, namely ST deviation. However, the score has not been developed exclusively for the risk stratification of STEMI patients. (Granger et al. 2003; Fox et al. 2006, 2014) Although it is recommended by the current guidelines to use the GRACE score for risk stratification in patients with STEMI, the score is not generally widely used (Fox et al. 2014; Byrne et al. 2023). Fox et. al suggested that one of the reasons for not using risk scores for risk evaluation might be the fact that the biomarker results may not be readily available during the initial presentation of the patients (Fox et al. 2014). The implementation

of additional ECG parameters – Q waves and TWI – into the GRACE score had an incremental prognostic value in the present study (Study I). Furthermore, ECG is readily available and a cornerstone of STEMI diagnosis. The evaluation of a STEMI patient's risk might be sufficiently achieved with the ECG risk markers. In fact, Koivumäki et al. showed that there is only modest variation in the evaluation of Q and T wave changes among physicians, making the evaluations reliable (Koivumäki et al. 2015).

In summary, the risk assessment of STEMI patients is improved with ECG analysis extending beyond STE, and risk assessment relying only on ECG analysis might be more feasible than using risk scores in the hectic clinical setting.

6.2.2 Location of MI

In previous studies, patients with an anterior MI had a worse outcome compared to patients with a non-anterior MI (Geltman et al. 1979; Stone et al. 1988; Kandzari et al. 2006). The present study showed that the risk of an adverse outcome in STEMI patients can be evaluated based on different ECG changes, regardless of the MI location. In Study I, the patients with EMI had more anterior infarcts than did patients with PIS. However, in multivariable analysis, the ECG change (EMI vs PIS) remained independently predictive irrespective of the location of the MI. Moreover, the location of the MI (non-anterior vs anterior) was not independently predictive of an adverse outcome when the EMI and PIS ECG changes were included in the analysis. In Study II, GI (G3I vs G2I) was also found to be an independent predictor of an adverse outcome regardless of the MI location. Patients with Q waves more often had an anterior MI compared to patients with no Q waves, and the same was true for patients with TWI (Study III). The location of the MI was not independently predictive, nor did it confound the effect of Q waves or TWI when analysed jointly or separately.

Larger IS has been regarded as the main factor behind the increased risk of an adverse outcome associated with an anterior MI (Geltman et al. 1979; Stone et al. 1988; Kandzari et al. 2006). MI patients with larger IS, as estimated by the degree of CK level elevation or detected by means of SPECT or CMR, were at an increased risk of death, re-infarction or HF (Sobel et al. 1972; Geltman 1984; Miller et al. 1995; Eitel et al. 2014). In the present study, a higher total CK level or elevated troponin level at presentation were not confined solely to patients with a high-risk ECG finding, and in Studies I and III, elevated troponin was not an independent predictor

of outcome when Q waves and TWI were considered. Therefore, it seems that larger IS in high-risk patients does not simply explain the results of the present study.

In summary, even though an anterior MI has been associated with adverse effects on the outcome, possibly due to a larger IS, the location of the MI seems to be irrelevant when more important factors, including high-risk ECG changes, are considered.

6.2.3 Time delays

It has been shown that a longer delay before treatment increases mortality among patients with a STEMI (De Luca et al. 2003, 2004; Brodie et al. 2006) and that a time from symptom onset of more than four hours is an independent predictor of 1-year mortality (De Luca et al. 2003). However, some studies have demonstrated that a longer time from symptom onset to treatment is not an independent predictor of mortality (Cannon et al. 2000; Antoniucci et al. 2002; Song et al. 2016), while the time from hospital arrival to treatment is (Cannon et al. 2000; Terkelsen et al. 2010). In Studies I and III, patients with Q waves and/or TWI had a longer time from symptom onset to treatment compared to patients without Q waves or TWI. In multivariable analysis (Study I), however, the time from symptom onset was not independently predictive, nor was it confounding towards the effect of ECG changes on the risk of an adverse outcome. In Study II among patients with G3I and G2I in the presenting ECG, the time from symptom onset to treatment was virtually the same, and similarly to Studies I and III, the time from symptom onset was not an independent predictor of outcome.

In summary, time delays during the course of a STEMI have an impact on patient management and outcome, and minimizing these delays is essential. However, when other important clinical factors, including high-risk ECG changes, are considered in the assessment of patient outcome, the effects of longer delays on the outcome are diminished.

6.3 ECG changes and prognosis

6.3.1 Pathological Q waves

The prevalence of pathological Q waves in STEMI patients at presentation has varied in previous studies. Raitt et al. described pathological Q waves at presentation to be a common finding among patients with an MI (Raitt et al. 1995). They reported a prevalence of 53%, while Birnbaum et al. reported a prevalence of 39% (Raitt et al. 1995; Birnbaum et al. 1997). Koivula et al. reported Q waves in 25% of patients, Kosmidou et al. in 40%, and Tiller et al. in as many as 53% (Koivula et al. 2019; Kosmidou et al. 2017; Tiller et al. 2019a). In the present study, the prevalence of pathological Q waves was 29% (Study III). The difference in the prevalence of Q waves between various studies might be related to different definitions of this ECG finding. Another possible explanation could be related to the number of patients included in the studies. For example, in Study III, the number of patients enrolled was 7,831, while in the studies conducted by Raitt et al. and Tiller et al., the numbers of patients were only 695 and 195, respectively (Raitt et al. 1995; Tiller et al. 2019a).

In Study III, the patients with Q waves had Killip class of 2 or higher more often than those without Q waves. The Killip classification is used to identify patients with different degrees of HF during an acute MI (AMI). Patients are stratified into four groups (I–IV), with class I signifying no HF and class IV signifying cardiogenic shock. (Killip and Kimball 1967) The Killip classification has been an independent predictor of in-hospital and 6-month mortality in patients with AMI, and patients with a higher Killip class have had a lower EF (DeGeare et al. 2001). Results from CMR studies have shown that patients with Q waves have a lower EF than patients without Q waves (Delewi et al. 2013; Tiller et al. 2019a). Despite the lack of EF evaluation by imaging modalities in the present study, the results are comparable with the CMR studies by Delewi et al. and Tiller et al. (Delewi et al. 2013; Tiller et al. 2019a), as the patients with Q waves more often had a Killip class of ≥ 2. In concert with a previous study (DeGeare et al. 2001), a Killip class of ≥ 2 was found to be an independent predictor of an adverse outcome in Studies I and III. However, the presence of pathological Q waves was independently predictive of an adverse outcome regardless of the presence of Killip class 2 or higher, and, therefore, it is reasonable to state that the effect of pathological Q waves on the outcome is not simply explained by a poorer EF.

Comparably to previous studies, TIMI 0 flow was more often seen in patients with pathological Q waves in the present study (Study III)(Wong et al. 1999; Tiller et al. 2019a). However, Wong et al. showed that, when more than three hours had elapsed since symptom onset, the prevalence of normal epicardial flow (TIMI 3 flow) was similar between patients with or without Q waves (30% vs 38%) (Wong et al. 1999). In the present study, TIMI 0 flow was not an independent predictor of outcome when the presence of Q waves was considered (Studies I and III). The effect of pathological Q waves on the outcome seems to prevail regardless of the epicardial flow status.

In Study III, patients with initial pathological Q waves had an increased risk of the composite of CV death, recurrent MI, NYHA class IV HF and cardiogenic shock compared to patients without Q waves. However, the effect was seen only in the time period ≤ 40 days. After 40 days, there was no statistical difference in the outcome between patients with or without Q waves. It seems that Q waves in the presenting ECG of STEMI patients have only a short-term effect on the outcome. This could possibly be explained by Q wave regression. Previous studies have shown that initial Q waves in STEMI patients may regress after reperfusion therapy (Bateman et al. 1983; Barold et al. 1987; Coll et al. 1988; Delewi et al. 2013; de Framond et al. 2019). Delewi et al. found that 40% of patients with initial Q waves had Q wave regression during 2-year follow-up, and in 10 out of 184 (5.4%) patients, the Q wave regression occurred during the first month of follow-up (Delewi et al. 2013). The regression of Q waves has been linked to better EF improvement and smaller IS as assessed by CMR, as well as to lower left ventricular end-diastolic pressure (LVEDP) (Delewi et al. 2013; de Framond et al. 2019; Coll et al. 1988). Moreover, the regression of Q waves might be a sign of the resolution of myocardial stunning and may, therefore, indicate a better outcome (Bateman et al. 1983; Barold et al. 1987).

In summary, despite pathological Q waves being linked to a variety of factors associated with an adverse outcome, the present study showed that pathological Q waves have an independent effect on the outcome. In addition, Q waves seem to affect only the early post-PCI outcome.

6.3.2 TWI

The prevalence of TWI at presentation was 8.5% in the present study (Study III). This is in line with previous studies – Koivula et al. and Herz et al. reported a TWI prevalence of 12.5% and 9%, respectively (Koivula et al. 2019; Herz et al. 1999).

An anterior location of the MI was more frequent in patients with TWI in the present study (Study III), and the same has been observed in previous studies, including those by Herz et al. and Hira et al. (Herz et al. 1999; Hira et al. 2014). However, as discussed in the previous section regarding the location of the MI, TWI was an independent predictor of an adverse outcome regardless of the MI location (Study III).

TIMI 0 flow was less frequently seen in patients with TWI than in patients with no TWI (59.5% vs 68.3%; $p < 0.001$) (Study III). A similar finding was reported in the study by Hira et al., where TIMI 0 flow was seen in 45.2% of patients with TWI compared to 64.3% of those with no TWI (Hira et al. 2014). In contrast, Wong et al. found that suboptimal epicardial flow (TIMI 0 to 2) was more often seen in patients with TWI, when patients were treated with FT, but the presence or absence of TWI was not an independent predictor of TIMI 3 flow (Wong et al. 1999). In the present study, TIMI 0 flow was not an independent predictor of an adverse outcome, when TWI was included in the analysis (Studies I and III).

There are conflicting results among previous studies regarding the effect of pre-procedure TWI on the outcome. Shimada et al. found that TWI in the presenting ECG was associated with a higher risk of the composite endpoint of death, recurrent MI, cardiogenic shock, TVR and HF during hospitalization (adjusted OR 2.8; 95% CI 1.1–7.0; $p = 0.027$), and TWI was an independent predictor of outcome regardless of the time from symptom onset (Shimada et al. 2013). In contrast, Herz et al. found that TWI was associated with in-hospital mortality only in patients treated after two hours from symptom onset (Herz et al. 1999). Koivula et al. did not find TWI without associated Q waves to be associated with 1-year mortality (Koivula et al. 2019). In the present study (Study III), the patients with TWI had a higher risk of the composite of CV death, recurrent MI, cardiogenic shock and HF, but only later than 40 days from the pPCI procedure. A similar finding was made by Koivula et al., who demonstrated that TWI without Q waves in the presenting ECG had an effect on late mortality, even though the effect was not statistically significant. Interestingly, in the present study, the risk of all-cause death within the time period of ≤ 40 days was elevated in patients with TWI (Study III), but this might be affected by the presence of Q waves.

In summary, similarly to pathological Q waves, TWI was an independent predictor of an adverse outcome in the present study, despite variation in other high-risk factors. The effect of TWI on the outcome was not evident until later after pPCI, with no effect on the early outcome.

6.3.3 PIS and EMI ECG patterns

In previous studies, patients with Q waves and/or TWI in the presenting ECG (the EMI pattern) had more anterior than non-anterior infarcts. The proportion of anterior MIs among patients with EMI was 74% in the study by Eskola et al. (Eskola et al. 2007) and 67% in the study by Koivula et al. (Koivula et al. 2019). The result of the present study is in line with the previous studies, as 60% of the EMI patients had anterior MIs (Studies I and III). However, in patients with an anterior MI, the prevalences of the EMI and PIS ECG patterns were virtually the same (52% and 48%, respectively). In multivariable analysis, patients with EMI had a worse outcome regardless of the location of the MI (Studies I and III).

TIMI 0 flow in the preprocedural angiogram was seen more often in patients with EMI than in those with PIS (70.6% vs 66%; $p < 0.001$) (Study I). In Study III, the prevalence of TIMI 0 flow was found to be highest among the patients with the Q+TWI- pattern and lowest in those with the Q-TWI+ pattern, while more than half of the patients in this group (54.8%) still had TIMI 0 flow, indicating non-patency of the infarct-related artery. Wong et al. reported that only 20% of patients with both Q waves and TWI in the ECG had TIMI 3 flow as a marker of normal epicardial flow, and the absence of Q waves was an independent predictor of TIMI 3 flow (Wong et al. 1999). In addition, in Study III, patients with the Q+TWI- pattern also most frequently showed a TIMI grade 5 thrombus (total occlusion) (72.3%), while the patients with the Q-TWI+ pattern had the lowest prevalence of TIMI grade 5 thrombi (54.5%). Furthermore, as seen in Studies I and III, the prevalence of TIMI grade 5 thrombi was rather high (64.7%) in patients with the Q-TWI- pattern (PIS). These findings suggests that pathological Q waves or TWI are not reliable indicators of the epicardial flow status or thrombus burden in STEMI patients. Also, the effect of these different ECG patterns on the outcome was independent regardless of TIMI 0 flow and TIMI grade 5 thrombi (Studies I and III).

In the present study (Study I), the patients with Q waves and/or TWI (EMI pattern) had a higher risk of the composite of CV death, recurrent MI, cardiogenic

shock and HF compared to patients without Q waves or TWI (PIS pattern) (aHR 1.54; 95% CI 1.30–1.82; $p < 0.001$). In Study III, it was shown that the risk was highest among patients with both Q waves and TWI (Q+TWI+). Q waves and TWI seemed to have a different temporal effect on the outcome, as the risk of an adverse outcome in patients with the Q+TWI+ and Q+TWI- patterns was elevated during the first 40 days of follow-up, but no additional risk was detected beyond 40 days, while the risk of an adverse outcome in patients with the Q-TWI+ pattern was elevated only during the time period of 41 days to 1 year.

The explanation for the poorer outcome in patients with Q waves and/or TWI, and for the different temporal effects, is probably multifactorial. One possible explanation could be related to MVO and IMH as detected by CMR. MVO and IMH have been linked to worse outcome in patients with STEMI (Eitel et al. 2014; van Kranenburg et al. 2014; Reinstadler et al. 2019). Eitel et al. found MVO to be associated with an increased risk of the composite of death, re-infarction and HF (major adverse cardiac events, MACE) within one year (adjusted OR 3.63; 95% CI 1.35–7.90; $p = 0.004$) (Eitel et al. 2014), while van Kranenburg et al. similarly demonstrated that MVO was associated with an increased risk of MACE within two years of follow-up (adjusted HR 3.74; 95% CI 2.21–6.34; $p < 0.001$) (van Kranenburg et al. 2014). Moreover, Reinstadler et al. showed that IMH was independently associated with MACE (adjusted HR 3.1; 95% CI 1.2–7.7; $p = 0.013$) (Reinstadler et al. 2019). Tiller et al. found that Q waves at presentation were strongly associated with MVO (Q wave vs no Q wave; adjusted OR 5.23; 95% CI 2.58–10.58; $p < 0.001$) and IMH detected by means of CMR (adjusted OR 3.94; 95% CI 1.83–8.46; $p < 0.001$) (Tiller et al. 2019a). TWI at presentation has not been studied comprehensively by CMR, but Reindl et al. found that patients with persisting TWI at four months had more MVO detected by means of CMR compared to patients without TWI at four months (Reindl et al. 2017). Pierard and Lancellotti also suggested that T-wave normalization within four months post-STEMI results in better functional recovery, as assessed by stress echocardiography, compared to patients with persisting TWI (Lancellotti et al. 2002). The possible explanation for the Q+TWI- and Q+TWI+ patterns affecting the outcome only within the time period of 40 days could be related to Q wave regression. Studies have shown that patients with Q wave regression experience more improvement in their EF (Delewi et al. 2013), in addition to having a smaller IS (de Framond et al. 2019) and lower LVEDP (Coll et al. 1988). Patients with MVO also have slightly higher LVEDP compared to patients without MVO (OR 1.05; 95% CI 1.02–1.08; $p < 0.05$) (Bonfig

et al. 2022). This could further indicate that a decrease in the degree of MVO results in a better outcome with the ECG finding of Q wave regression.

In summary, patients with the EMI pattern (Q waves and/or TWI) in their ECG have a higher risk of an adverse outcome when compared to patients with the PIS (no Q wave or TWI) pattern, while the highest risk was found in patients with the Q+TWI+ pattern. The Q+TWI- and Q+TWI+ patterns affected the outcome only within 40 days, and the Q-TWI+ pattern only after 40 days.

6.3.4 Grade of ischemia

The prevalence of G3I on the presenting ECG in STEMI patients with positive T waves was 22% in the present study (Study II). This is in line with previous studies; in a study by Sejersten et al., the distribution of G2I (73%) and G3I (27%) was similar to our study (Sejersten et al. 2006).

In the present study, patients with G3I more often had a Killip class of ≥ 2 at admission compared to patients with G2I (5.1% vs 3.5 %, $p = 0.006$) (Study II). A similar finding was made by Birnbaum et al., who reported the prevalence of a Killip class >1 to be higher in patients with G3I than in those with G2I (19.5% vs 15.6%, $p = 0.01$) (Birnbaum et al. 1996a). However, some studies have not found this difference in the admission Killip class between G3I and G2I patients (Lee et al. 2001; Sejersten et al. 2006; Garcia-Rubira et al. 2008). While Killip class was found to be higher in patients with G3I in Study II, there was no difference between G3I and G2I patients regarding the risk of new or worsening NYHA IV HF or cardiogenic shock within one year. In addition, G3I was an independent predictor of adverse outcome regardless of Killip class in multivariable analysis.

TIMI 0 flow was slightly more frequent in patients with G3I (73.5% vs 66.9% with G2I; $p < 0.001$) in Study II. Sejersten et al. demonstrated a similar finding: 69% of the patients with G2I had low TIMI flow (0 to 1), which is comparable to the present study (Sejersten et al. 2006). In a study by Birnbaum et al., there was no difference in the initial TIMI flow between G3I and G2I patients (Birnbaum et al. 2001). In the present study (Study II), TIMI 0 flow was not an independent predictor of outcome, nor did it confound the effect of GI classification on the outcome. Poor collateral flow (Lee et al. 2001; Garcia-Rubira et al. 2008) and the absence of preinfarction angina (Celik et al. 2008) has been suggested as factors contributing to more severe ischemia in G3I patients. However, Sejersten et al. did not find any correlation between collateral flow and GI, while Birnbaum et al. reported the

prevalence of preinfarction angina to be similar in G3I and G2I patients (Sejersten et al. 2006; Birnbaum et al. 2001). It seems that epicardial flow status does not explain the different GIs, and the pathophysiological background is more complex.

In the CMR studies by Weaver et al. and Rommel et al., G3I was associated with more extensive MVO (expressed as % of LV mass) and IMH (Weaver et al. 2011; Rommel et al. 2016). However, the number of patients with MVO did not differ between the G3I and G2I patients (55% vs 48%, $p = 0.15$) (Rommel et al. 2016). Moreover, in the study by Rommel et al., only the risk of re-infarction was found to be higher among patients with G3I (5.5% vs 1.8% with G2I; $p = 0.02$), while the risk of all-cause death and new HF did not differ between these two patient groups. In addition, neither of these studies considered the possible effect of pathological Q waves on the development of MVO or IMH. In the present study (Study II), pathological Q waves were more often seen in patients with G3I than in those with G2I (35.1% vs 24.8%; $p < 0.001$), and both pathological Q waves and G3I were found to be independent predictors of an adverse outcome.

In summary, G3I is an independent risk factor of poor outcome regardless of other factors, including the presence of pathological Q waves.

6.4 The effect of routine aspiration thrombectomy

Earlier studies regarding the effect of the use of routine aspiration thrombectomy on the angiographic and clinical outcome measures had suggested better STR and myocardial microcirculatory perfusion (assessed by myocardial blush grade) compared to PCI alone (Burzotta et al. 2005; De Luca et al. 2006b; Silva-Orrego et al. 2006; Svilaas et al. 2008). The ECG analyses in these studies only considered changes in the ST segment without analysing Q waves, TWI or the GI. Moreover, none of these studies detected a significant reduction in adverse clinical outcomes with the use of routine thrombectomy. Vlaar et al. showed that routine aspiration thrombectomy resulted in a lower risk of CV death or reinfarction (adjusted OR 0.54; 95% CI 0.33–0.93; $p = 0.025$) (Vlaar et al. 2008). However, two large trials assessing the benefit of routine aspiration thrombectomy, the TASTE trial (Fröbert et al. 2013; Lagerqvist et al. 2014) and the TOTAL trial (Jolly et al. 2015, 2016), did not find differences between the thrombectomy and PCI alone groups regarding death, re-infarction or HF during up to 1 year of follow-up. Furthermore, the TOTAL trial demonstrated that patients undergoing routine thrombectomy had a higher risk of stroke than patients in the PCI alone group (Jolly et al. 2015, 2016).

A CMR study conducted by Sardella et al. showed that STEMI patients undergoing routine aspiration thrombectomy had a lower rate of MVO as assessed three to five days after reperfusion therapy, when compared to patients undergoing PCI alone (31.5% vs 72.9%, $p < 0.001$), but at three months' follow-up, MVO was not seen in any of these patient groups (Sardella et al. 2009). The only ECG parameter considered in that study was STR, with no assessment of other dynamic ECG changes. As more extensive MVO is associated with the presence of pathological Q waves (Tiller et al. 2019a) and G3I (Weaver et al. 2011) at presentation, it could be assumed that these high-risk patients would benefit from routine aspiration thrombectomy. The present study (Studies I, II and III), however, demonstrated that routine aspiration thrombectomy did not lower the risk of the composite of CV death, re-infarction, cardiogenic shock or NYHA IV HF in any of the high-risk patient groups. Even though there was a trend towards a benefit from routine thrombectomy in the Q+TWI+ subgroup regarding the risk of the primary outcome, the result was not statistically significant (9.9% vs 15.8%; HR 0.60; 95% CI 0.31–1.15) (Study III). However, the number of Q+TWI+ patients was rather small (142 patients in the thrombectomy group and 171 patients in the PCI alone group), and it could be speculated that this might explain the failure to reach statistical significance.

In summary, routine aspiration thrombectomy is not beneficial to STEMI patients in general, as shown by Jolly et al. (Jolly et al. 2015, 2016), and there is no clear benefit from thrombectomy even in high-risk subgroups based on ECG findings.

6.5 Impact of the present study on current risk assessment

As the present study showed, evaluating the 12-lead ECG recorded at presentation of STEMI for changes in the Q wave, the terminal portion of the QRS complex and the T wave in addition to STE has an impact on individual risk assessment in STEMI. Identifying STEMI patients with the lowest (Q-TWI-, Figure 7 A) and the highest (Q+TWI+, Figure 7 D) risk of an adverse outcome could be particularly helpful in, for example, to triaging multiple STEMI patients presenting simultaneously for pPCI.

6.6 Limitations

There are some limitations to the present study. Firstly, although the statistical analyses considered numerous confounding factors, some unmeasured confounding factors may still exist and affect the results.

Secondly, while the number of patients in the present study was one of the highest ever enrolled for STEMI-ECG studies, the numbers of patients in the Q-TWI+ and Q+TWI+ groups in Study III were rather small (354 and 313, respectively) and the analyses may lack power, especially since the follow-up was split into two time periods.

Thirdly, in Study III, TWI was considered as a categorical variable, including patients with deep, fully negative T waves as well as those with biphasic T waves with only a small negative terminal portion, which could have affected the results.

Fourthly, post-PCI ECGs were not analysed for the present study. Therefore, STR, T-wave normalization or Q wave regression after PCI were not considered, although they could provide insight into possible risk variation between different patient groups stratified by pre-PCI and post-PCI ECG changes.

A further limitation is that, while the initial TIMI flow grade 0 was not an independent predictor of outcome in the present study (Studies I, II and III), data on post-PCI TIMI flow grade were not collected, and its possible correlation to the ECG changes could therefore not be assessed.

Furthermore, data on peak CK, troponin or CMR were not collected, and as a result, IS could not be properly assessed, despite the possibility that this could have been one of the potential explanations for the differences in risk between the patient groups in the present study.

Finally, as Aslanger et al. have shown, ACS patients with an occlusive MI, but without significant STE, have a high risk of short-term and long-term mortality when compared to patients with a non-occlusive MI (Aslanger et al. 2020, 2021). For the ECG analyses in the present study, only patients with a significant STE were included, and, therefore, the possible effect of pathological Q waves, TWI or distortion of the terminal portion of the QRS complex on the risk of an adverse outcome in the case of non-significant STE could not be evaluated.

6.7 Future perspectives

Although timely reperfusion therapy is essential when treating STEMI patients, different therapeutical approaches for patients with varying risks of an adverse outcome, as assessed by the ECG changes, have not been studied to a notable degree, and the decision between pPCI and FT is currently based on time delays. As was demonstrated by the present study, the time from symptom onset to treatment did not influence the outcome when the ECG changes were considered. Previously, Eskola et al. found that patients who had an anterior STEMI with pathological Q waves and without TWI had a better outcome with pPCI than with FT (Eskola et al. 2007), while Birnbaum et al. showed that the difference in the outcome of G2I and G3I patients was consistent regardless of the treatment strategy (pPCI or FT) (Birnbaum et al. 2001). In the future, it would be of interest to determine whether pPCI or FT would result in a different outcome in the high-risk patient groups, as assessed by the ECG changes, outside the currently set system delay of 120 minutes for pPCI.

Even though the risk evaluation of STEMI patients can be achieved reliably by the assessment of different ECG changes, no prospective, controlled studies have randomized STEMI patients to different therapeutic strategies based on the GI or EMI/PIS classification. Therefore, there are currently no real opportunities to tailor therapy based on these ECG parameters. Hypothetically, more efficient anti-remodelling and anti-thrombotic therapies should be used in patients who are at the highest risk of an adverse outcome. Future studies should consider these ECG-based risk categories when assessing tailored treatments.

7 SUMMARY AND CONCLUSIONS

Risk assessment in STEMI patients can be performed by evaluating changes observed in the conventional 12-lead ECG. The use of rather complex risk assessment tools and risk scores can be time-consuming in everyday clinical settings, and individual risk assessment of a STEMI patient is often disregarded. Therefore, simple and efficient methods for risk assessment are clearly needed. The present study has shown that the presenting ECG can be used for risk assessment, in addition to its important role in the diagnosis of STEMI. The major findings and conclusions are as follows:

1. The assessment of a patient's risk in STEMI can be improved by incorporating pathological Q waves and TWI in the risk assessment in addition to the conventional ECG variable STE and clinical risk factors.

2. G3I is an independent predictor of an adverse outcome regardless of the presence of pathological Q waves.

3. Pathological Q waves and TWI are independent risk factors for an adverse outcome, and in patients with both Q waves and TWI, the risk of an adverse outcome is the highest. Pathological Q waves seem to have a more short-term and TWI a more long-term effect on the outcome.

4. Routine aspiration thrombectomy was not beneficial even in patients with a high risk of an adverse outcome, as assessed by the ECG changes.

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PUBLICATIONS

PUBLICATION I

The high-risk ECG pattern of ST-elevation myocardial infarction: A substudy of the randomized trial of primary PCI with or without routine manual thrombectomy (TOTAL trial).

Leivo J, Anttonen E, Jolly SS, Džavík V, Koivumäki J, Tahvanainen M, Koivula K, Nikus K, Wang J, Cairns JA, Niemelä K, Eskola MJ.

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The high-risk ECG pattern of ST-elevation myocardial infarction: A substudy of the randomized trial of primary PCI with or without routine manual thrombectomy (TOTAL trial)

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ABSTRACT

Background: Useful tools for risk assessment in patients with STEMI are needed. We evaluated the prognostic impact of the evolving myocardial infarction (EMI) and the preinfarction syndrome (PIS) ECG patterns and determined their correlation with angiographic findings and treatment strategy.
Methods: This substudy of the randomized Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) included 7860 patients with STEMI and either the EMI or the PIS ECG pattern. The primary outcome was a composite of death from cardiovascular causes, recurrent MI, cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within one year.
Results: The primary outcome occurred in 271 of 2618 patients (10.4%) in the EMI group vs. 322 of 5242 patients (6.1%) in the PIS group [AdjustedHR, 1.54; 95% CI, 1.30 to 1.82; $p < .001$]. The primary outcome occurred in the thrombectomy and PCI alone groups in 131 of 1306 (10.0%) and 140 of 1312 (10.7%) patients with EMI [HR 0.94; 95% CI, 0.74–1.19] and 162 of 2633 (6.2%) and 160 of 2609 (6.1%) patients with PIS [HR 1.00; 95% CI, 0.81–1.25], respectively ($p_{interaction} = 0.679$).
Conclusions: Patients with the EMI ECG pattern proved to have an increased rate of the primary outcome within one year compared to the PIS pattern. Routine manual thrombectomy did not reduce the risk of primary outcome within the different dynamic ECG patterns. The PIS/EMI dynamic ECG classification could help to triage patients in case of simultaneous STEMI patients with immediate need for pPCI.

1. Introduction

Primary percutaneous coronary intervention (pPCI) is the treatment of choice for patients with acute ST-elevation myocardial infarction (STEMI) [1]. The electrocardiographic (ECG) hallmark of sudden coronary artery occlusion is ST-segment elevation (STE), while inverted T waves and Q waves represent later stages of the infarct process. To distinguish between these two entities, the concepts of "preinfarction syndrome" (PIS) and "evolving myocardial infarction" (EMI) were introduced. The PIS is defined as STE with a positive T wave without pathological Q waves, while in EMI, STE is accompanied with pathological Q waves and/or T wave inversion (TWI). [2] In a previous study, patients with EMI had worse outcome than patients with the PIS ECG pattern when treated with either fibrinolytic therapy (FT) or pPCI [3].

The Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) demonstrated that routine aspiration thrombectomy did not reduce the risk for adverse outcome in patients undergoing pPCI [4,5]. Several ECG substudies, including the

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PIS/EMI comparison, of the TOTAL trial were prespecified [6]. The aims of the present study were to assess the prognostic significance of the dynamic EMI and PIS ECG patterns to determine their correlation with angiographic findings and to explore whether routine manual thrombectomy is beneficial for patients with either the EMI or the PIS ECG pattern.

2. Methods

2.1. Patients and randomization

The TOTAL trial included 10,732 patients with STEMI. The inclusion and exclusion criteria for the trial have been described previously. The patients were randomly assigned into two treatment groups: manual aspiration thrombectomy followed by PCI or PCI alone. The study protocol included the recording of a pre-procedure ECG in all eligible patients. [4,6]

All of the ECGs from the TOTAL trial were analyzed in the ECG core laboratory at the Heart Center, Tampere University Hospital, where all investigators were blinded to the treatment assignment, including clinical and angiographic findings. For this substudy, we identified all patients, who had undergone the index PCI and had a baseline ECG available ($n = 10{,}064$) and then excluded those with: left bundle branch block ($n = 62$), other broad QRS >120 ms ($n = 486$), poor technical quality of the ECG ($n = 703$) and STEMI ECG criteria not fulfilled ($n = 953$). The final study population included 7860 patients.

2.2. Study outcomes

The definitions of outcomes have been described in detail previously [4–6]. The primary outcome was a composite of cardiovascular death, recurrent MI, cardiogenic shock or new or worsening New York Heart Association (NYHA) class IV heart failure within one year. Key secondary outcomes were the primary outcome plus stent thrombosis or target-vessel revascularization within one year. All-cause mortality within one year was also defined as a secondary outcome. The key safety outcome was stroke within one year, and the net risk-benefit outcome was a composite of the primary outcome and the key safety outcome within one year.

2.3. ECG analysis

STE was measured from the J point using the TP segment as the isoelectric line. As investigators were unaware of the patients' age and gender, a modified cut-point of 0.2 mV for STE in leads V2–V3 was used. For all the other leads, the guideline-based cut-point of ≥0.1 mV in two or more contiguous leads were used [7]. The STEMI location was defined as anterior, inferior and lateral or other based on the location of the STE in leads V1–V6; II, III, aVF; and I, aVL, V5–V6, respectively. Regarding STE in the precordial leads, patients were classified as lateral in case of STE only in V5 and V6. If any of the leads V1–V4 showed STE in addition to leads V5 or V5 and V6, the classification was anterior. The "lateral or other" group also included the patients, where the cut-off values of STE were fulfilled for both anterior and inferior STE. Pathological Q waves were defined as any Q wave of 0.02 s or more in duration or a QS complex in leads V2 and/or V3. Regarding other leads, a Q wave ≥0.03 s and ≥ 0.1 mV was considered as pathological when present in ≥2 contiguous leads [7]. Q waves in leads aVR, III and V1 were not taken into account.

The PIS was defined as STE without TWI or pathological Q waves in the leads with STE, while EMI was defined as STE with TWI and/or pathological Q waves in the leads with STE (Supplementary Fig. 1). The definition of TWI was either a fully negative T wave or a biphasic T wave with a ≥ 0.05 mV negative terminal portion.

2.4. Statistical analyses

Categorical variables were represented as counts and percentages whereas continuous variables were represented as the mean ± standard deviation, or as the median with interquartile range (IQR). Differences between groups were assessed by the Chi-square test for categorical variables, and two-sample *t*-test and Wilcoxon rank-sum tests for normally and non-normally distributed continuous variables, respectively. The Cox regression model was used to assess the effect of dynamic ECG changes on the risk of primary and secondary outcomes. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. The cumulative incidences of the primary outcome and of cardiovascular death were charted using Kaplan-Meier curves. In adjusted multivariable analysis, age and symptom onset were forced into the model given their clinical importance; gender, location of MI, current smoking, hypertension, diabetes mellitus, previous MI, previous PCI, proximal lesion (lesion located at least in one of the following: [1] Right coronary artery (RCA) origin, [2] RCA proximal including right ventricle, [3] Left main coronary artery, [4] 3 mm after origin of left anterior descending (LAD), [5] Left circumflex proximal, [6] LAD proximal (first 3 mm of the proximal LAD)), heart rate, Killip class ≥2, elevated troponin, Thrombolysis In Myocardial Infarction (TIMI) flow 0 before PCI, Thrombus grade (5 vs. <5), symptom-onset-to-balloon time (per 10 min increment) and cardiogenic shock were tested for inclusion based on their influence on overall model fit and confounding effects. A backward elimination approach was implemented to sequentially remove baseline risk factors with *p*-values >.05, starting from those with the highest p-value. To identify potential confounders, all previously dropped risk factors were individually added back to the model and remained in the model if the effect size of ECG pattern changed by >10%. As a sensitivity analysis, a propensity score matching approach was implemented to control for confounding effects. All the aforementioned covariates in multivariable analysis were included in the propensity score model. EMI and PIS patients were matched in a ratio of 1:1 with caliper width set to 0.2 of pooled standard deviation of logit of propensity score [8]. Standardized difference was used to evaluate the matching quality and a value of <0.1 was considered as a negligible difference between groups. Cox regression with robust standard errors was applied to account for the matched nature of data. To evaluate the incremental prognostic value of ECG pattern when added to the Global Registry of Acute Coronary Events (GRACE) score, two multivariable Cox models were constructed: [1] a conventional model including components of GRACE score: age, heart rate, systolic blood pressure, Killip class, creatinine, non-fatal cardiac arrest and elevated troponin (ST-segment deviation was not considered as it was the inclusion criterion for TOTAL population) and [2] a working model including ECG pattern in addition to the GRACE score components. These two models were compared with the likelihood ratio test. The discriminatory capacity of the two models was assessed by C-statistic. The risk reclassification capacity due to the addition of ECG pattern was evaluated by continuous Net Reclassification Index (NRI) and relative Integrated Discrimination Improvement (IDI) [9]. 95% confidence interval was constructed with 1000 bootstrap sample. Unless otherwise specified, A 2-tailed *p* value of <0.05 was considered statistically significant. All analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

The baseline characteristics of the study patients are shown in Table 1. Male gender was more frequent in patients with EMI. They also had slightly higher heart rate and blood pressure, more often Killip class ≥2, a longer time from symptom onset to hospital arrival and a longer door-to-balloon time and more often elevated troponin at admission compared with patients having PIS. Patients with PIS had marginally higher body mass index and more frequent use of bivalirudin, enoxaparin and upfront glycoprotein IIb/IIIa inhibitor.

Table 1
Baseline characteristics according to dynamic ECG changes.

Characteristics[a]	EMI, $n = 2618$	PIS, $n = 5242$	p value
Age (years)	60.8 ± 12.0	60.6 ± 11.8	0.465
Male gender	2092 (79.9)	3985 (76.0)	<0.001
Heart Rate (bpm)	80.1 ± 17.8	74.3 ± 16.9	<0.001
Systolic blood pressure (mmHg)	136.7 ± 26.2	134.7 ± 26.5	0.001
Diastolic blood pressure (mmHg)	84.2 ± 16.6	81.7 ± 16.4	<0.001
BMI (kg/m^2)	27.2 ± 4.5	27.8 ± 4.7	<0.001
Killip class ≥2	142 (5.4)	164 (3.1)	<0.001
Location of MI			<0.001
Anterior	1580 (60.4)	1480 (28.2)	
Inferior	944 (36.1)	3494 (66.7)	
Lateral or other	92 (3.5)	265 (5.1)	
Elevated troponin at admission	1771 (67.6)	2833 (54.0)	<0.001
Medical history			
Previous Stroke	72 (2.8)	155 (3.0)	0.606
Hypertension	1280 (48.9)	2604 (49.7)	0.513
Diabetes	449 (17.2)	944 (18.0)	0.348
Previous MI	250 (9.5)	433 (8.3)	0.056
Previous PCI	213 (8.1)	423 (8.1)	0.919
Peripheral arterial disease	61 (2.3)	108 (2.1)	0.437
Current smoker	1195 (45.6)	2408 (45.9)	0.807
Time to initial PCI procedure			
Symptom onset to hospital arrival (min)	142.0 (82.0–252.0)	114.0 (66.0–190.0)	<0.001
Door-to-balloon (min)	55.0 (25.0–90.0)	48.0 (21.0–85.0)	<0.001
Medication use			
Unfractionated heparin	2207 (84.3)	4287 (81.8)	0.005
Bivalirudin	453 (17.3)	1017 (19.4)	0.025
Enoxaparin	185 (7.1)	453 (8.6)	0.016
Glycoprotein IIb/IIIa inhibitor			
Upfront	626 (23.9)	1380 (26.3)	0.021
Bailout	418 (16.0)	766 (14.6)	0.114
Initial TIMI thrombus grade[b]			0.052
0: no thrombus	62 (2.4)	135 (2.6)	
1: possible thrombus	108 (4.1)	278 (5.3)	
2: definitive thrombus, <0.5 x vessel diameter	64 (2.4)	153 (2.9)	
3: definitive thrombus, 0.5–2.0 x vessel diameter	267 (10.2)	556 (10.6)	
4: definitive thrombus, >2.0 x vessel diameter	330 (12.6)	727 (13.9)	
5: total occlusion	1786 (68.2)	3390 (64.7)	
TIMI 0 flow before PCI[c]	1847 (70.6)	3462 (66.0)	<0.001
Upfront manual thrombectomy	1278 (48.8)	2544 (48.5)	0.812
Bailout thrombectomy	105 (4.0)	183 (3.5)	0.248
Duration of PCI procedure (min)	37.0 (27.0–51.0)	36.0 (27.0–50.0)	0.138

EMI, evolving myocardial infarction; PIS, preinfarction syndrome; bpm, beats per minute; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Values are given as counts and percentage; mean ± SD or median and interquartile range.

[b] The thrombus grade is measured as the largest dimension of the thrombus as compared with the diameter of the vessel in which it occurs.

[c] TIMI flow graded on a scale of 0 to 3, with a higher grade indicating better flow.

Anterior location of MI was more often seen in the EMI group, while inferior MI was more frequent in patients with PIS. Regarding medical history, there were no differences between the two groups. There was a trend to higher initial TIMI thrombus grade in the EMI group ($p = .052$). Patients with EMI more often had totally occluded infarct related artery (TIMI 0 flow) before the index PCI. Procedure time did not differ between the two groups.

The effect of dynamic ECG changes on the risk of primary outcome and cardiovascular death is shown in Fig. 1. The primary outcome at one year follow-up was more frequent in the patients with EMI, compared to those with PIS [271 (10.4%) vs. 322 (6.1%); HR, 1.73; 95% CI, 1.47 to 2.03; $p < .001$, respectively]. This was also true for cardiovascular death [131 (5.0%) vs. 127 (2.4%); HR, 2.10; 95% CI, 1.64 to 2.68; $p < .001$], cardiogenic shock [75 (2.9%) vs. 69 (1.3%); HR, 2.21; 95% CI, 1.59 to 3.06; $p < .001$] and class IV heart failure [73 (2.8%) vs. 75 (1.4%); HR, 1.99; 95% CI, 1.44 to 2.74; $p < .001$] when analyzed separately. There was no difference in recurrent MI between the two groups [73 (2.8%) with EMI vs. 124 (2.4%) with PIS; HR, 1.20; 95% CI 0.90 to 1.60; $p = .223$]. Furthermore, event rates for the key secondary outcome and all-cause mortality were higher in the EMI group [358 (13.7%) vs. 505 (9.6%); HR, 1.46; 95% CI, 1.27 to 1.67; $p < .001$ and 149 (5.7%) vs. 166 (3.2%); HR, 1.83; 95% CI 1.46 to 2.28; $p < .001$, respectively]. There was no difference in the key safety outcome (stroke within one year) between the EMI and PIS groups [25 (1.0%) vs. 44 (0.8%); HR, 1.16; 95% CI, 0.71 to 1.89; $p = .559$]. The net risk-benefit outcome (the primary outcome plus stroke within one year) occurred in 281 (10.7%) of the patients in the EMI group and 348 (6.6%) of the patients in the PIS group (HR, 1.66; 95% CI, 1.42 to 1.94; $p < .001$).

The results of the adjusted multivariable analysis are shown in Table 2. The ECG pattern of EMI predicted worse outcome compared with PIS (Adjusted HR, 1.54; 95% CI, 1.30 to 1.82; $p < .001$). In contrast to the other variables in the model, location of MI (non-anterior vs. anterior), current smoking, hypertension, previous PCI, elevated troponin, TIMI 0 flow before PCI and symptom-onset-to-balloon time (per 10 min increment) were neither independently predictive nor confounding regarding the effect of dynamic ECG change, and were therefore excluded from the final model.

In the propensity score analysis, 1848 EMI patients were matched to 1848 PIS patients. After matching, all the selected variables showed a good balance between EMI and PIS groups (Supplementary Table 1). The primary outcome occurred in 194 patients (10.5%) in the EMI group and 139 (7.5%) in the PIS group (HR 1.43; 95% CI, 1.15 to 1.77; $p = .001$).

ECG pattern showed a significant incremental prognostic value when added to the GRACE score by the likelihood ratio test ($p < .001$). A modest increase in C-statistic was detected after adding the ECG pattern (0.712; 95% CI, 0.688 to 0.735 and 0.719; 95% CI, 0.694 to 0.742; $p = .088$, for GRACE score alone and GRACE score with ECG pattern, respectively). Both continuous NRI and relative IDI support the incremental prognostic value of ECG pattern (0.279; 95% CI, 0.192 to 0.368 and 0.085; 95% CI, 0.048 to 0.125, respectively).

As shown in Table 3 the effects of routine thrombectomy compared with PCI alone on the primary outcome and its components did not differ between the EMI and PIS groups.

4. Discussion

We conducted a prospective, prespecified substudy of the TOTAL trial, including 7860 STEMI patients, and demonstrated that STE accompanied by Q waves and/or TWI (EMI) was associated with worse outcome than STE alone (PIS) in the presenting ECG at one-year follow-up.

"Hyperacute" positive T waves develop within minutes from coronary artery occlusion, and are immediately followed by STE if the artery remains occluded [10,11]. The PIS ECG pattern was associated with better outcome than the EMI pattern at 2.7-year follow-up in the Danish Trial in Acute Myocardial Infarction-2 (DANAMI-2) trial [3]. In the present study, the prognostic significance of these ECG patterns was evaluated for the first time in a prospective manner. TWI and Q waves are considered later ECG markers of the infarction process than STE [11], and the rationale behind the division into PIS and EMI patterns is based on these temporal pathophysiological aspects.

4.1. The preinfarction syndrome and evolving MI

Originally, PIS was considered as a very early manifestation of myocardial ischemia presenting before the development of myocardial

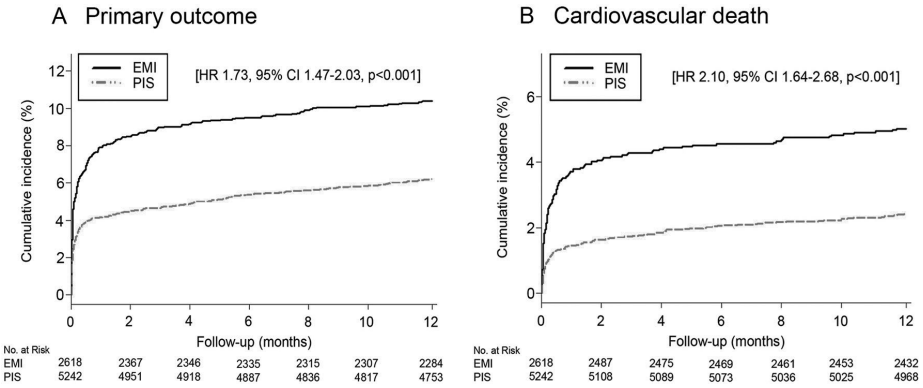

Fig. 1. Kaplan-Meier estimates of the primary outcome (death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association class IV heart failure) (Panel A) and cardiovascular death (Panel B) in patients with preinfarction syndrome (PIS) and evolving myocardial infarction (EMI) within one year.

Table 2
Adjusted multivariable analysis of the effect of dynamic ECG changes and other variables on the risk of primary outcome.

	HR (95% CI)	*p* value
Dynamic ECG change (EMI vs. PIS)	1.54 (1.30–1.82)	<0.001
Age, per 10 year increment	1.51 (1.41–1.63)	<0.001
Symptom onset (6–12 h vs. <6 h)	1.12 (0.91–1.38)	0.302
Gender (female)	1.38 (1.16–1.66)	<0.001
Diabetes	1.67 (1.39–2.01)	<0.001
Previous MI	1.61 (1.27–2.04)	<0.001
Proximal lesion [a]	1.22 (1.03–1.43)	0.020
Heart rate, per 10 bpm increment	1.16 (1.11–1.21)	<0.001
Killip class ≥2	1.78 (1.34–2.36)	<0.001
Thrombus grade (5 vs. <5)	1.19 (1.00–1.41)	0.050
Cardiogenic shock	3.41 (2.11–5.49)	<0.001

EMI, evolving myocardial infarction; PIS, preinfarction syndrome; MI, myocardial infarction.
[a] Lesion located at least in one of the following: (1) Right coronary artery (RCA) origin, (2) RCA proximal including right ventricle, (3) Left main coronary artery, (4) 3 mm after origin of left anterior descending (LAD), (5) Left circumflex proximal, (6) LAD proximal (first 3 mm of the proximal LAD).

injury, while EMI would represent a later stage of the disease process [2]. In the present study, worse outcome of the patients with EMI was not explained by longer symptom-onset-to-balloon time, infarct location or TIMI flow at the time of angiography. It seems evident that the difference in outcome between these ECG patterns is not simply explained by differences in time for the disease process. Regarding the two ECG changes contained in the EMI pattern, Q waves could be a marker of larger ischemic area, more intense ischemia, microvascular injury or myocardial stunning, while TWI could indicate dynamic changes in coronary flow with potential for distal microembolization and also microvascular injury or myocardial stunning [12–17]. However, it was not the purpose of this study to explore possible pathophysiologic background factors for PIS and EMI, and we can only speculate on the issue.

4.2. Inverted T waves in STEMI

Although new-onset TWI after FT or pPCI is regarded as a marker of improved outcome, the significance of TWI at presentation is not well-defined [18,19]. In a study with a small number of patients, TWI in the leads with maximal STE was associated with a higher prevalence of patency of the infarct-related artery, especially in patients with anterior STEMI [20].

On the other hand, in patients treated with FT ($n = 2853$), TWI in the leads with STE upon admission was associated with adverse outcome in patients presenting >2 h after symptom onset, whereas in patients presenting within two hours, TWI indicated a better outcome [21]. Also, TWI persisting four months post-STEMI was independently associated with more extensive myocardial damage by cardiac magnetic resonance (CMR) imaging, and showed a worse outcome [17,22]. A recent study showed that TWI was related to the presence of myocardial edema in patients with NSTE-ACS. However, only isolated TWI and isolated ST depression were independently predictive of myocardial edema, while ST depression with TWI was not. [23]

Table 3
Effect of treatments on primary outcome and components, subgrouped by EMI/PIS.

Outcomes	Subgroup	Thrombectomy[a]	PCI alone[a]	HR (95% CI)	*p* value[b]
Primary outcome	EMI	131/1306 (10.0)	140/1312 (10.7)	0.94 (0.74–1.19)	0.679
	PIS	162/2633 (6.2)	160/2609 (6.1)	1.00 (0.81–1.25)	
CV death	EMI	62/1306 (4.7)	69/1312 (5.3)	0.90 (0.64–1.27)	0.478
	PIS	66/2633 (2.5)	61/2609 (2.3)	1.07 (0.76–1.52)	
Recurrent MI	EMI	36/1306 (2.8)	37/1312 (2.8)	0.97 (0.61–1.54)	0.872
	PIS	60/2633 (2.3)	64/2609 (2.5)	0.93 (0.65–1.32)	
Cardiogenic shock	EMI	43/1306 (3.3)	32/1312 (2.4)	1.35 (0.85–2.14)	0.025
	PIS	27/2633 (1.0)	42/2609 (1.6)	0.63 (0.39–1.03)	
Class IV heart failure	EMI	38/1306 (2.9)	35/1312 (2.7)	1.09 (0.69–1.72)	0.770
	PIS	41/2633 (1.6)	34/2609 (1.3)	1.20 (0.76–1.89)	

EMI, evolving myocardial infarction; PIS, preinfarction syndrome; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a] Values are given as no. of events/no. of patients (%).
[b] P value for interaction is from likelihood ratio test of interaction term, using unadjusted Cox regression model.

4.3. Q waves in the ECG at presentation

The presence of pathological Q waves at presentation independently predicts a worse.

outcome after FT or pPCI and is associated with a larger infarct size in CMR [12,24,25]. In a study with consecutive STEMI patients ($n = 2290$), 36.9% had Q waves on their baseline ECG. Baseline Q waves, but not time to reperfusion, were associated with increased odds of an in-hospital composite end point. The type of reperfusion did not modify the association of baseline Q waves with in-hospital outcomes. [26]

4.4. ECG-based risk scores

Guidelines recommend using the GRACE risk score for the risk stratification in the acute phase of STEMI before reperfusion therapy. However, the GRACE score includes only one (crude) ECG parameter: ST deviation. [1,27] In the present study we found, that a different pattern of ECG at STEMI presentation gives important incremental prognostic value in addition to the conventional risk factors (GRACE score).

An objective ECG method for quantifying the timing of evolving acute MI, the Anderson–Wilkins (A-W) acuteness score, was developed and later modified [28,29]. The A-W score was superior to treatment delay (time from pain-to-balloon) in predicting final infarct size, salvage and mortality in STEMI patients [30]. While the A-W score has been proved to be superior to historical timing in predicting outcome in patients with STEMI, it is considered too time-consuming for manual interpretation, and despite the creation of automated algorithms, it is not widely used in clinical settings [31,32]. Our study results show that important prognostic information is to be gained from the ECG at presentation by adding simple ECG parameters – TWI and Q waves – to the well-documented parameter STE. Furthermore, the EMI and PIS ECG patterns are reliably identified by cardiologists, and can be easily adopted by junior doctors [33].

4.5. Location of STE and PIS vs. EMI

In our study, patients with EMI more often had anterior STEMI, while PIS patients more often presented with inferior infarcts. This unequal distribution could be due to differences in ECG classification of Q and T waves between the anterior and inferior leads or to different pathophysiological mechanisms of STEMI at different locations. The influence of infarct location and different cut-off values for ECG parameters have proved to be important in previous works as well. Hedén et al. pointed out the need for adjustment of the cut-off value for pathological Q waves, in order to synchronize the performance of the A-W score in anterior and inferior MI [29]. Bao et al. showed that, depending on the location of STE, modified cut-off values added prognostic value in predicting clinical outcomes in comparison with standard criteria for the classification of pathological Q waves [34]. According to Fakhri et al., the applicability of ECG indices of severity and acuteness of myocardial ischemia to estimate myocardial damage and salvage potential in STEMI patients treated with pPCI was confined to anterior MI. [30] In general, anterior MIs are larger than inferior MIs; in the present study, however, we showed that the PIS/EMI classification was an independent predictor of outcome, regardless of the MI location.

4.6. Predictors of outcome

The patients in the EMI category had a higher heart rate, higher Killip class, more often elevated troponin and a longer symptom-onset-to-balloon time. There was a trend towards a higher initial TIMI thrombus grade in EMI than in PIS patients ($p = .052$), and EMI patients more often had a totally occluded culprit artery (TIMI flow 0) on angiography. In multivariable analysis, dynamic ECG change, age, gender, diabetes, previous MI, proximal lesion location, higher heart rate, Killip class ≥2, higher thrombus grade, and cardiogenic shock were independent predictors of outcome. Accordingly, dynamic ECG change had an important prognostic impact independently of the symptom-onset-to-balloon time. According to previous studies, a longer time from symptom onset predicted worse outcome [35–38]. However, when adjusting for more important clinical factors, the time from symptom onset seemed to be irrelevant in our analyses. This highlights the importance of an expanded role of the ECG in risk stratification. It could also be pointed out that patient-reported time of symptom onset may not be a reliable marker for the time point of coronary artery occlusion [3].

No studies have compared different therapeutic approaches based on ECG-based risk scores or dynamic ECG changes. However, the PIS pattern ($n = 952$) was associated with lower composite endpoint of death, clinical re-infarction, or disabling stroke in STEMI patients treated with pPCI compared with FT [3]. Previous studies have shown that routine manual thrombectomy did not reduce the risk for adverse outcome in patients with STEMI [4,5]. In addition, our study showed that routine manual thrombectomy did not reduce the risk for adverse outcome even if patients were stratified into different risk groups by ECG pattern.

We are not able to give any recommendations regarding tailoring of treatment in individual patients based on the EMI/PIS classification. This would require studies, where the patients would be randomized into different treatment strategies based on the ECG pattern. Hypothetically, patients with the EMI pattern should have more efficient antithrombotic and anti-remodeling therapy than patients, who present with the PIS pattern. However, we have identified a high-risk subgroup, and we think that the implementation of guideline-recommended therapeutic measures is particularly important in these patients.

4.7. Limitations

In the present study, the prognostic role of Q waves and inverted T waves was not analyzed separately. While our analyses were adjusted for accounted confounders, some unmeasured confounders may still exist and influence the results. Furthermore, we did not have the data for post-PCI TIMI flow or ST-segment resolution which could have influenced the results.

5. Conclusions

In a large STEMI patient population, an ECG pattern with Q waves and/or inverted T waves (EMI) in the acute phase was associated with a higher rate of cardiovascular death, recurrent MI, cardiogenic shock, or NYHA class IV heart failure within one year as compared to ST elevation without Q waves or T wave inversions (the PIS pattern). Routine manual thrombectomy, as compared with PCI alone, did not reduce the risk of primary outcome within the different dynamic ECG patterns. The PIS/EMI dynamic ECG classification was an independent predictor of outcome.

The simple PIS/EMI dynamic ECG classification is useful for risk assessment and could help for example to triage simultaneously presenting STEMI patients with immediate need for pPCI. The prognostic role of Q waves and inverted T waves should be evaluated separately in further studies.

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Disclosures

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II

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The prognostic significance of grade of ischemia in the ECG in patients with ST-elevation myocardial infarction: A substudy of the randomized trial of primary PCI with or without routine manual thrombectomy (TOTAL trial)

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ABSTRACT

Background: The importance of the grade of ischemia (GI) ECG classification in the risk assessment of patients with STEMI has been shown previously. Grade 3 ischemia (G3I) is defined as ST-elevation with distortion of the terminal portion of the QRS complex in two or more adjacent leads, while Grade 2 ischemia (G2I) is defined as ST-elevation without QRS distortion. Our aim was to evaluate the prognostic impact of the GI classification on the outcome in patients with STEMI.

Methods: 7,211 patients from the TOTAL trial were included in our study. The primary outcome was a composite of cardiovascular death, recurrent myocardial infarction (MI), cardiogenic shock, or New York Heart Association (NYHA) class IV heart failure within one year.

Results: The primary outcome occurred in 153 of 1,563 patients (9.8%) in the G3I group vs. 364 of 5,648 patients (6.4%) in the G2I group (adjusted HR 1.27; 95% CI, 1.04 - 1.55; p=0.022). The rate of cardiovascular death (4.8% vs. 2.5%; adjusted HR 1.48; 95% CI 1.09 - 2.00; p=0.013) was also higher in patients with G3I.

Conclusions: G3I in the presenting ECG was associated with an increased rate of the composite of cardiovascular death, recurrent MI, cardiogenic shock, or NYHA class IV heart failure within one year compared to patients with G2I. Patients with G3I also had a higher cardiovascular death compared to patients with G2I.

Introduction

Extending the ECG interpretation beyond analysis of the ST-T changes improves prognostic assessment in acute myocardial infarction. In the Sclarovsky-Birnbaum ischemia grading system, the ECG changes are divided into three groups based on the severity of ischemia. In Grade 1 ischemia there are tall and peaked T waves without ST-elevation. In Grade 2 ischemia (G2I) there is ST-elevation without distortion of the terminal portion of the QRS complex, while in Grade 3 ischemia (G3I), ST-elevation is accompanied by distortion of the terminal portion of the QRS complex in two or more adjacent leads (1,2). The electrophysiological mechanism of QRS distortion is not yet well understood but animal study data suggested severe myocardial ischemia related to an injury of the ventricular Purkinje fibers (3).

In the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL), routine thrombectomy did not

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reduce the risk for adverse outcome (4,5). Different ECG substudies, including this substudy of the TOTAL trial were pre-planned (6). The rationale behind this study was based on the fact that the GI has been shown to be an important prognostic ECG marker. The aims of this study were to assess the prognostic impact of the GI in the pre-procedure ECG and its correlation to the angiographic data and treatment assignment.

Material and methods

Study population

The TOTAL trial included 10,732 patients. The patients were randomized into two treatment groups: manual aspiration thrombectomy followed by PCI or PCI alone. The inclusion and exclusion criteria for the study were described previously; all patients should have a pre-procedure ECG recording according to the study protocol (4,6).

All of the ECGs in the TOTAL trial were analyzed in the ECG core laboratory at the Heart Center, Tampere University Hospital. The investigators in the ECG core laboratory were blinded to the treatment groups and to all the clinical and angiographic findings. For this substudy we selected all patients who were treated either with manual aspiration thrombectomy and PCI or PCI alone and had a pre-procedure ECG available (n=10,064). According to the definition of ischemia grading, we excluded patients with left bundle branch block (n=62), other broad QRS >120 ms (n=486) and T wave inversions (n=649). Other reasons for exclusion from this sub-study were ECGs of poor technical quality (n=703) and those, where the STEMI ECG criteria were not fulfilled (n=953). Based on this, we included 7,211 patients in our analyses.

Study outcomes

The primary outcome was a composite of cardiovascular death, recurrent MI, cardiogenic shock or new or worsening New York Heart Association (NYHA) class IV heart failure within one year. Secondary outcomes were the primary outcome plus stent thrombosis or target-vessel revascularization (TVR) and all-cause mortality within one year. The safety outcome was stroke or transient ischemic attack (TIA) within one year, and the net risk-benefit outcome was a composite of the primary outcome and stroke within one year.

ECG analyses

All of the ECGs were recorded using 12-lead configuration. ST-elevation (STE) measurements were done from the J point using the TP segment as the isoelectric line. For STEMI diagnosis, a guideline-based cut-point of 0.1 mV in two or more adjacent leads was used for all other leads except for leads V2 and V3 where a cut-point of 0.2 mV was used (7). Based on the location of the STEs, STEMI was categorized as anterior (V1-V6), inferior (II, III, aVF) or lateral/other (I, aVL, V5-V6). A fully negative T wave or a biphasic T wave with ≥0.05 mV negative terminal portion were classified as T wave inversion. Pathological Q waves were defined as any Q wave ≥0.02 sec in duration or a QS complex in leads V2-V3 or as a Q wave ≥0.03 sec in duration and ≥0.1 mV in depth in two or more adjacent leads in all the other leads. As shown in Fig. 1, G3I was defined as absence of the S wave in rS-type complexes and as a J point amplitude ≥50% of the height of the R wave in qR-type complexes in two or more adjacent leads. G2I was defined as sustained S wave in rS-type complexes and as a J point amplitude <50% of the height of the R wave in qR-type complexes. In anterior QS-type complexes, the ECG was defined as G3I if there was a positive notch after the negative wave and G2I if the S wave continues into the ST-segment without any positive notch in two or more adjacent leads (Fig. 1, panel 3a and 3b).

Statistical analyses

Categorial variables were displayed as counts and percentages while continuous variables were displayed as the mean ± standard deviation, or as the median with interquartile range (IQR). Chi-square test was used to assess the differences between groups for categorical variables, and two-sample t-test and Wilcoxon rank-sum test were used for normally and non-normally distributed continuous variables, respectively. The Cox regression model was used to evaluate the effect of GI on the risk of primary and secondary outcomes. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Kaplan-Meier curves were used to chart cumulative incidence for the primary outcome and cardiovascular death. The analyses of primary and secondary outcomes were adjusted for pre-specified risk factors and confounders, including age, symptom onset (6-12hrs vs. <6hrs), gender, location of MI, current smoking, hypertension, diabetes mellitus, previous MI, previous PCI,

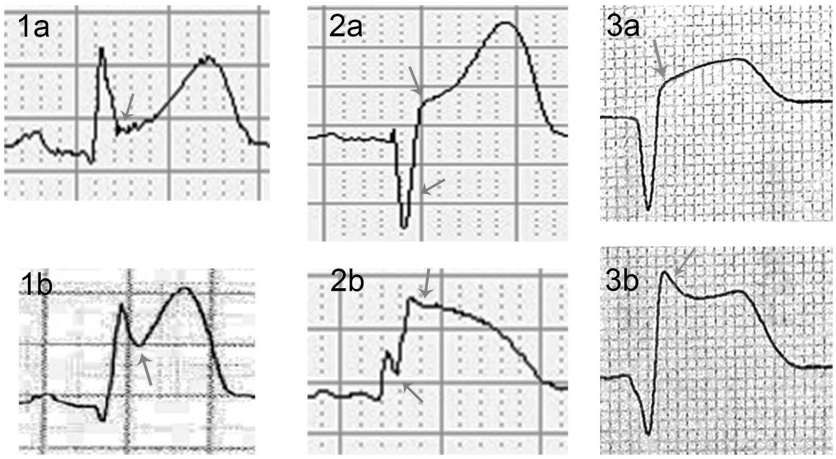

Fig. 1. In qR type complexes the amplitude of the J point (red arrows) is <50 % of the amplitude of the R wave in G2I (panel 1a) and ≥50 % in G3I (panel 1b). In rS type complexes S wave (green arrows) is present in G2I (panel 2a) and absent in G3I (panel 2b). In anterior QS-type complexes G2I is defined with the S wave continuing into the ST-segment without a positive notch (panel 3a) and in G3I there is a positive notch after the negative wave (panel 3b).

proximal lesion, heart rate, Killip class ≥2, TIMI flow 0 before PCI, Thrombus grade (5 vs. <5), time from symptom onset to procedure, cardiogenic shock, pathological Q waves for baseline ECG, systolic blood pressure, creatinine and cardiac arrest. The proportional hazards assumption of the Cox model and linearity of continuous variables were assessed using Schoenfeld residuals and restricted cubic spline plots, respectively. As a sensitivity analysis, propensity score matching was conducted using the same set of baseline variables. One G3I patient was matched to up to 3 G2I patients. Cox regression with robust standard errors was implemented in the propensity-matched cohort to account for the matched nature of the data. To identify the independent predictors of the primary outcome with a parsimonious model, age and symptom onset were forced into the model given their clinical importance, and all other abovementioned variables were tested for inclusion in the model based on their influence on overall model fit. Variables with p-value >0.05 were sequentially removed from the model using backward elimination approach. Likelihood ratio test was used to evaluate the interaction effect between grade of ischemia and routine thrombectomy compared with PCI alone on the primary outcome in Cox regression model. A two-sided p value of <0.05 was considered statistically significant with no adjustment of multiple testing considering the exploratory nature of the study. SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA) was used to perform all analyses.

Results

Table 1 shows the baseline and procedural characteristics. The patients with G3I were slightly older, had slightly higher heart rate and systolic blood pressure compared to patients with G2I. There were no differences regarding gender, diastolic blood pressure or body mass index between the two groups. The patients with G3I also more often had Killip class 2 or higher, pathological Q waves in the presenting ECG and a higher rate of inferior infarcts compared to patients with G2I. Regarding medical history, there were no differences between the two groups except for the fact that patients with G3I more often had hypertension. The number of patients with elevated troponin was virtually the same in the two groups. The time from symptom onset to hospital arrival was slightly longer in the G3I group, but there was no difference in time from hospital arrival to the invasive procedure. Radial access was used less often in patients with G3I. The patients with G3I were slightly more often treated with unfractionated heparin and less often with bivalirudin than patients with G2I. There was no difference in upfront usage of glycoprotein IIb/IIIa inhibitor between the two groups. In contrast, a glycoprotein IIb/IIIa inhibitor was slightly more often used as bailout in patients with G3I. The patients with G3I more often had TIMI thrombus grade 5 and TIMI flow 0 before the index PCI compared to patients with G2I. Bailout thrombectomy was used slightly more in patients with G3I. The median duration of the PCI procedure did not differ between the two groups.

The primary outcome occurred in 153 of 1563 patients (9.8%) with G3I and 364 of 5648 patients (6.4%) with G2I [adjusted HR 1.27; 95% CI 1.04 - 1.55; p=0.022]. When analyzed separately, the rates for cardiovascular death [75 (4.8%) vs. 143 (2.5%); adjusted HR 1.48; 95% CI 1.09 - 2.00; p=0.013] and recurrent MI [52 (3.3%) vs. 123 (2.2%); adjusted HR 1.54; 95% CI 1.11 - 2.16; p=0.013] were higher in patients with G3I compared to patients with G2I, respectively. We did not detect statistically significant difference between G3I and G2I regarding cardiogenic shock [38 (2.4%) vs. 89 (1.6%); adjusted HR 1.14; 95% CI 0.76 - 1.71; p=0.544], NYHA class IV heart failure [39 (2.5%) vs. 92 (1.6%); adjusted HR 1.24; 95% CI 0.84 - 1.84; p=0.282] or all-cause mortality [82 (5.2%) vs. 186 (3.3%); adjusted HR 1.25; 95% CI 0.94 - 1.65; p=0.128]. The results for primary and secondary outcomes are shown in Table 2. The effect of GI on the risk of the primary outcome and cardiovascular death is shown in Fig. 2.

In propensity score analysis, 1490 G3I patients were matched to 4135 G2I patients. All the selected baseline variables were well balanced between G3I and G2I groups after matching (Supplementary Table 1). The analysis of effect of GI on primary and secondary outcomes using propensity-matched cohort yielded comparable results to the multivariable adjusted analysis (Supplementary Table 2).

In the analysis of predictors for the primary outcome, grade of ischemia (G3I vs. G2I) remained an independent predictor. Other independent predictors were age, gender, location of MI (anterior vs. non-anterior), diabetes, previous MI, heart rate, Killip class ≥2, prior cardiogenic shock, pathological Q waves in the baseline ECG, systolic blood pressure (negatively associated), creatinine and cardiac arrest. In contrast, time from symptom onset to procedure, TIMI 0 flow before pPCI, TIMI thrombus grade (5 vs. <5), current smoking, hypertension, previous PCI and proximal lesion were not independently predictable and were therefore excluded from the final model. The results of the multivariable analysis of independent predictors for primary outcome are shown in Table 3.

Table 1
Baseline and procedural characteristics of patients according to grade of ischemia

Characteristics[a]	Grade 3 (N=1563)	Grade 2 (N=5648)	p value†
Age, years	61.5±11.6	60.3±11.8	<0.001
Gender (Male)	1222 (78.2)	4383 (77.6)	0.626
Heart Rate (beats per minute)	77.7±17.6	75.4±17.1	<0.001
Systolic blood pressure (mmHg)	133.6±26.3	135.7±26.2	0.006
Diastolic blood pressure (mmHg)	82.3±16.5	82.5±16.4	0.787
Body mass index (BMI, kg/m^2)	27.7±4.5	27.6±4.6	0.743
Killip class ≥2	79 (5.1)	200 (3.5)	0.006
Q-waves for baseline ECG	548 (35.1)	1403 (24.8)	<0.001
Location of MI			<0.001
Anterior	591 (37.8)	2138 (37.9)	
Inferior	929 (59.4)	3209 (56.8)	
Lateral or other	42 (2.7)	297 (5.3)	
Medical history			
Previous Stroke	54 (3.5)	149 (2.6)	0.084
Hypertension	808 (51.7)	2745 (48.6)	0.030
Diabetes	262 (16.8)	984 (17.4)	0.542
Previous MI	136 (8.7)	492 (8.7)	0.990
Previous PCI	128 (8.2)	461 (8.2)	0.972
Peripheral arterial disease	40 (2.6)	111 (2.0)	0.147
Current smoker	712 (45.6)	2613 (46.3)	0.618
Elevated troponin	887 (56.7)	3246 (57.5)	0.610
Time to initial PCI procedure			
Onset to Hospital (min)	123.0 (75.0-210.0)	119.0 (70.0-200.0)	0.008
Hospital to procedure (min)	50.0 (22.0-83.0)	49.0 (21.0-85.0)	0.843
Radial access	1006 (64.4)	3845 (68.1)	0.006
Medication use			
Unfractionated heparin	1317 (84.3)	4617 (81.7)	0.021
Bivalirudin	260 (16.6)	1104 (19.5)	0.009
Glycoprotein IIb/IIIa inhibitor			
Upfront	419 (26.8)	1447 (25.6)	0.343
Bailout	266 (17.0)	814 (14.4)	0.011
Initial TIMI thrombus grade[b]			0.003
0	29 (1.9)	143 (2.5)	
1	55 (3.5)	290 (5.1)	
2	34 (2.2)	157 (2.8)	
3	144 (9.2)	597 (10.6)	
4	195 (12.5)	754 (13.3)	
5	1106 (70.8)	3703 (65.6)	
TIMI 0 flow before PCI[c]	1149 (73.5)	3776 (66.9)	<0.001
Bailout thrombectomy	80 (5.1)	177 (3.1)	<0.001
Median PCI procedure time (min)	37.0 (27.0-51.0)	36.0 (27.0-50.0)	0.315

MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

[a] Values are given as counts and percentage; mean ± SD or median and interquartile range.

[b] The thrombus grade is measured as the largest dimension of the thrombus as compared with the diameter of the vessel in which it occurs.

[c] TIMI flow graded on a scale of 0 to 3, with a higher grade indicating better flow.

Table 2
Primary and secondary outcomes at 1 year, according to effect of grade of ischemia

Outcomes	Grade 3 (N=1563)	Grade 2 (N=5648)	Unadjusted		Adjusted[a]	
			HR (95% CI)	P Value	HR (95% CI)	P Value
Primary outcome and components						
Primary outcome	153 (9.8%)	364 (6.4%)	1.55 (1.29-1.88)	<0.001	1.27 (1.04-1.55)	0.022
Cardiovascular death	75 (4.8%)	143 (2.5%)	1.92 (1.45-2.54)	<0.001	1.48 (1.09-2.00)	0.013
Recurrent MI	52 (3.3%)	123 (2.2%)	1.56 (1.13-2.16)	0.010	1.54 (1.11-2.16)	0.013
Cardiogenic shock	38 (2.4%)	89 (1.6%)	1.55 (1.06-2.28)	0.028	1.14 (0.76-1.71)	0.544
Class IV Heart failure	39 (2.5%)	92 (1.6%)	1.56 (1.07-2.26)	0.025	1.24 (0.84-1.84)	0.282
CVD, MI, Cardiogenic shock, HF, Stent thrombosis, TVR	199 (12.7%)	572 (10.1%)	1.28 (1.09-1.51)	0.003	1.10 (0.93-1.31)	0.268
All-Cause Mortality	82 (5.2%)	186 (3.3%)	1.62 (1.25-2.10)	<0.001	1.25 (0.94-1.65)	0.128
Stent Thrombosis	52 (3.3%)	94 (1.7%)	2.04 (1.45-2.86)	<0.001	1.85 (1.30-2.62)	<0.001
Definite stent Thrombosis	41 (2.6%)	67 (1.2%)	2.25 (1.52-3.32)	<0.001	2.13 (1.42-3.19)	<0.001
Target vessel revascularization	93 (6.0%)	302 (5.3%)	1.13 (0.90-1.43)	0.297	1.11 (0.87-1.41)	0.395
Major bleeding	28 (1.8%)	99 (1.8%)	1.03 (0.68-1.57)	0.882	0.89 (0.57-1.37)	0.589
Safety outcome						
Stroke	15 (1.0%)	43 (0.8%)	1.28 (0.71-2.30)	0.420	1.38 (0.75-2.54)	0.315
TIA	2 (0.1%)	13 (0.2%)	0.56 (0.13-2.50)	0.418	0.47 (0.10-2.19)	0.301
Net risk-benefit risk outcome						
CVD, MI, Cardiogenic Shock, HF, Stroke	162 (10.4%)	387 (6.9%)	1.55 (1.29-1.86)	<0.001	1.29 (1.06-1.57)	0.012

MI, myocardial infarction; CVD, cardiovascular death; HF, heart failure; TVR, target vessel revascularization; TIA, transient ischemic attack.
[a] Adjusted for age, symptom onset (6-12hrs vs. <6hrs), gender, location of MI, current smoking, hypertension, diabetes, previous MI, previous PCI, proximal lesion, heart rate, Killip class ≥2, TIMI 0 flow before PCI, Thrombus grade (5 vs. < 5), time from symptom onset to procedure, prior cardiogenic shock and Q-wave for baseline ECG, systolic BP, creatinine and cardiac arrest

The effect of routine thrombectomy compared to PCI alone on the primary outcome did not differ between patients with G3I and G2I [10.2% vs. 9.4%; HR 1.08; 95% CI 0.79 - 1.49 for G3I group and 6.3% vs. 6.6%; HR 0.95; 95% CI 0.77 - 1.17 for G2I group; p for interaction = 0.496]. The effect of routine thrombectomy compared to PCI alone on the primary outcome did not differ between the symptom onset groups (<6 hours vs. 6-12 hours) when analyzed separately in G3I and G2I patients. The results for the effect of treatments are shown in Supplementary Table 3.

Discussion

This prospective, pre-planned substudy of the TOTAL trial showed that G3I in the pre-procedure ECG is associated with a worse clinical outcome compared to G2I. Several previous studies have assessed the prognostic implications of the GI in patients with STEMI. However, the present study, which included 7,211 patients, is to our knowledge the largest prospective study dealing with this ECG classification.

The electrophysiological mechanism of distortion of the terminal portion of the QRS complex is not yet well understood; although a study done with porcine hearts suggested altered conduction velocity in the Purkinje fibers (3). Moreover, it has been speculated that ischemia has to be severe to affect the Purkinje fibers. Results from a study using single-photon emission computed tomography indicated more severe ischemia in G3I than in G2I. (1,3,8) Furthermore, poor myocardial protection due to absence of preinfarction angina (preconditioning) and insufficient collateral flow were proposed as possible background factors for QRS distortion (9–11).

The effect of GI on outcome

In 1993, the first study conducted by Birnbaum et al to study the correlation of different GIs on in-hospital mortality, included 147 patients with anterior MI treated with thrombolytic therapy. The study showed a clear association between different GIs and mortality. (1) The association was confirmed in later studies of patients with QRS distortion treated with thrombolytic therapy, and G3I also was an independent predictor of increased in-hospital mortality (2,12). STEMI patients treated with pPCI, who had QRS distortion in the initial ECG proved to have higher in-hospital and 30-day mortality compared to patients

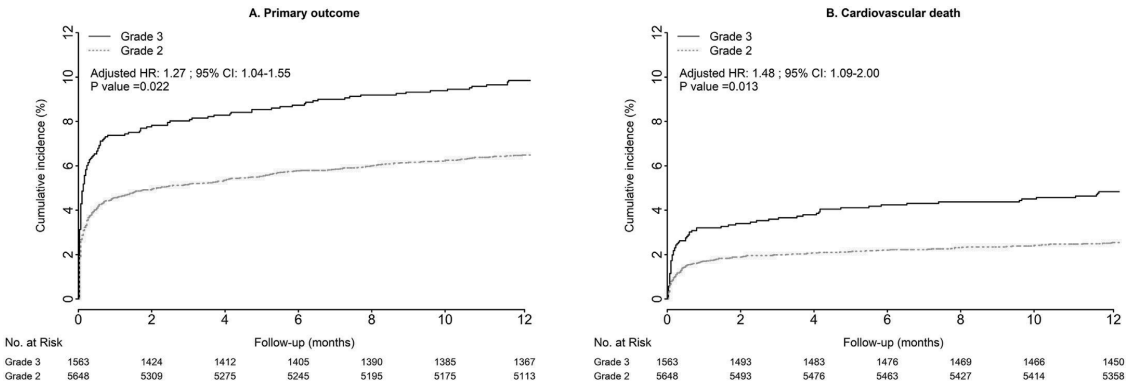

Fig. 2. Kaplan-Meier estimates of the primary outcome (death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association class IV heart failure) (Panel A) and cardiovascular death (Panel B) in patients with Grade 3 ischemia and Grade 2 ischemia within one year.

Table 3
Multivariable analysis of independent predictors for the risk of primary outcome

	HR (95% CI)	p value
Grade of ischemia (Grade 3 vs. Grade 2)	1.28 (1.05-1.56)	0.017
Age, per 10 year increment	1.47 (1.35-1.59)	<0.001
symptom onset (6-12hrs vs. <6hrs)	1.19 (0.93-1.51)	0.168
Gender (female)	1.46 (1.20-1.78)	<0.001
Location of MI (anterior vs. non-anterior)	1.28 (1.06-1.56)	0.012
Diabetes	1.68 (1.37-2.05)	<0.001
Previous myocardial infarction	1.44 (1.11-1.87)	0.008
Heart rate, per 10 bpm increment	1.16 (1.11-1.22)	<0.001
Killip class ≥2	1.62 (1.19-2.19)	0.003
Prior cardiogenic shock	2.10 (1.19-3.70)	0.018
Q-waves in the baseline ECG	1.43 (1.17-1.75)	<0.001
Systolic BP, per 10 mm Hg increment	0.92 (0.88-0.95)	<0.001
Creatinine, per 1 mg/dL increment	1.29 (1.15-1.44)	<0.001
Cardiac arrest	4.82 (3.22-7.22)	<0.001

MI, myocardial infarction; BP, blood pressure.

without QRS distortion (13,14). Studies have also confirmed the association between G3I and the risk for recurrent MI and failure of ST-segment resolution (13,15–17). The present study corroborates the results of previous studies, and additionally it showed that G3I predicts higher 1-year cardiovascular death in patients treated with pPCI; this was also shown in a previous study of patients treated with thrombolysis for anterior STEMI and one study showed higher long-term mortality in patients with G3I treated with thrombolytic therapy or pPCI (12,18).

Numerous studies have shown that G3I predicts larger infarcts and impaired myocardial salvage (8,11,15,19–22). As a consequence, patients with G3I tend to have a higher incidence of heart failure but this was not demonstrated in our present study (15). We found no significant difference between the G2I and G3I patients regarding elevated troponin. This could be explained simply by the fact that only admission laboratory values were included in our study and therefore we were unable to assess the infarct size of G2I and G3I patients.

Pathological Q waves

Pathological Q waves in the presenting ECG during STEMI are independent predictors of higher mortality, cardiogenic shock and congestive heart failure (23–25). They also predict larger infarcts and impaired reperfusion (26,27). In the present study, pathological Q waves were more frequently seen in patients with G3I, which is in line with previous studies (14,20). According to a previous study, G3I was independently associated with infarct size regardless of the presence of pathological Q waves (20). We found that G3I is an independent predictor of poor outcome regardless of the presence of pathological Q waves in the pre-procedure ECG.

Location of MI

We found that patients with G3I had more inferior infarcts compared to patients with G2I. There was virtually no difference between G3I and G2I regarding anterior infarcts. Whether this is related to differences in ECG criteria between anterior and inferior infarct location or a true difference between these STEMI categories needs to be explored in future studies. In general, anterior infarcts are larger than infarcts in other locations, resulting in worse outcome. In a previous study, worse outcome in patients with G3I was confined only to anterior infarcts, whereas in the present study patients with G3I had worse outcome regardless of the location of MI (12). Therefore, it seems that the prognostic significance of G3I is not explained solely by a larger infarct size.

Time of symptom onset

According to the prevailing guidelines, patients with STEMI should undergo reperfusion therapy as expeditiously as possible (28). Study results are inconclusive regarding the prognostic significance of time from symptom onset to reperfusion therapy: the results from some studies indicate that STEMI patients with a longer time delay have worse outcome, while other studies found no clear evidence for an independent role of time delays (29–34). Previous studies showed that compared to patients with G2I, those with G3I have higher in-hospital and 30-day mortality and less myocardial salvage when presenting late - two to three hours from symptom onset - but not when presenting earlier (2,20,35). In the present study, time from symptom onset to reperfusion therapy was not an independent predictor of outcome, although the patients with G3I had slightly longer time delays than the patients with G2I. On the other hand, G3I was an independent predictor of poor outcome regardless of time delays. This seems to support the hypothesis that G3I represents more severe ischemia. It should also be noted that the exact time of onset of symptoms might be difficult to identify due to the patient-recall bias and the dynamic pathophysiologic nature of acute coronary events.

Reperfusion treatment strategy

The TOTAL trial concluded that routine manual thrombectomy was not superior to pPCI with respect to patient outcome as a whole (4,5). Previous studies have shown that there is no difference in mortality between pPCI and thrombolytic therapy when the comparison is based on the GI classification (13,35). The present study demonstrated that neither G3I nor G2I patients benefit from routine manual thrombectomy compared to pPCI alone. This was also true even when the effect of routine thrombectomy compared to pPCI alone on the primary outcome was assessed between different ischemic time groups separately in G3I and G2I patients. Based on our results, it is not possible to give any recommendations concerning modification of the treatment for patients with different GIs. Prospective randomized studies with different therapeutic strategies based on the GI in the presenting ECG would be required to test any hypothesis in this regard.

Limitations

Although we adjusted our analyses for a number of confounding variables, residual confounding due to unmeasured risk factors might still exist and affect the study results. We did not have the data for peak or 48/72 hour troponin and therefore we could not assess the infarct size. A recent study assessed the diagnostic accuracy of ECG predicting acute coronary occlusion beyond the standard STEMI criteria. The study results indicated that it is possible to recognize high-risk patients with occlusive MI from the initial ECG even when STEMI criteria per current guidelines are not fulfilled. It was also shown that patients with acute coronary occlusion MI (ACOMI), with or without ST-elevation, have higher risk for larger infarcts and higher short term and long term mortality. The authors even suggest renaming STEMI/NSTEMI as OMI/non-OMI. (36,37) The present study included only patients fulfilling standard STEMI criteria and therefore it is impossible to make any conclusions whether patients with G3I would have a higher risk for adverse outcome when the STEMI criteria are not fulfilled.

Conclusions

The present study comprising one of the largest STEMI patient population ever published, showed that patients with G3I on the pre-procedure ECG have a higher risk for composite of cardiovascular death, recurrent MI, cardiogenic shock or NYHA class IV heart failure within one year compared to patients with G2I. Moreover, G3I proved to be an independent predictor of outcome regardless of pathological

Q waves or time from symptom onset to invasive therapy. Routine manual thrombectomy did not reduce the risk for adverse outcome in patients with G3I or G2I. The GI classification is a useful tool for risk assessment in acute STEMI.

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Appendix A. Supplementary data

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PUBLICATION III

The prognostic significance of Q waves and T wave inversions in the ECG of patients with STEMI: A substudy of the TOTAL trial.

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ABSTRACT

Background: The prognostic significance of Q waves and T-wave inversions (TWI) combined and separately in STEMI patients undergoing primary PCI has not been well established in previous studies.
Methods: We included 7,831 patients from the TOTAL trial and divided the patients into categories based on Q waves and TWIs in the presenting ECG. The primary outcome was a composite of cardiovascular death, recurrent myocardial infarction (MI), cardiogenic shock or new or worsening NYHA class IV heart failure within one year. The study evaluated the effect of Q waves and TWI on the risk of primary outcome and all-cause death, and whether patient benefit of aspiration thrombectomy differed between the ECG categories.
Results: Patients with Q+TWI+ (Q wave and TWI) pattern had higher risk of primary outcome compared to patients with Q-TWI- pattern [33 (10.5%) vs. 221 (4.2%); adjusted hazard ratio (aHR) 2.10; 95% CI, 1.45-3.04; p<0.001] within 40-days' period. When analyzed separately, patients with Q waves had a higher risk for the primary outcome compared to patients with no Q waves in the first 40 days [aHR 1.80; 95% CI, 1.48-2.19; p<0.001] but there was no additive risk after 40 days. Patients with TWI had a higher risk for primary outcome only after 40 days when compared to patients with no TWI [aHR 1.63; 95% CI, 1.04-2.55; p=0.033]. There was a trend towards a benefit of thrombectomy in patients with the Q+TWI+ pattern.
Conclusions: Q waves and TWI combined (Q+TWI+ pattern) in the presenting ECG is associated with unfavourable outcome within 40-days. Q waves tend to affect short-term outcome, while TWI has more effect on long-term outcome.

Introduction

Both pathological Q waves and T wave inversions (TWI) in the presenting ECG of patients with ST elevation myocardial infarction (STEMI) have an impact on patient outcome. Pathological Q waves have been more consistently associated with worse outcome compared to TWI [1–10]. Numerous pathophysiological mechanisms may be involved in the development of Q waves and TWI in patients with STEMI. The Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) showed that routine aspiration thrombectomy was not superior to PCI alone as a treatment strategy in STEMI patients [11,12]. In this substudy of the TOTAL trial, our objectives were to investigate the prognostic significance of Q waves and TWI combined and separately, and whether the patient benefit from routine aspiration

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thrombectomy differs between various combinations of Q waves and TWI.

Material and methods

Study population

A total of 10,732 patients were enrolled in the TOTAL trial. The inclusion and exclusion criteria have been described in detail previously [11,12]. The patients of the TOTAL trial had STEMI with symptoms of myocardial ischemia and time from symptom onset ≤ 12 hours, had a pre-procedure ECG and underwent primary percutaneous coronary intervention (PCI) with or without manual aspiration thrombectomy after randomization to these two groups. Different ECG substudies of the TOTAL trial, including this one, were pre-planned [11,13]. All the study ECGs were analyzed at the Heart Hospital, Tampere University Hospital by the ECG core laboratory investigators, who were blinded to clinical and angiographic data, as well as treatment assignment. For this substudy we selected all patients who had a pre-procedure ECG available and had an index invasive coronary artery procedure done (n=10,064). Patients with left bundle branch block (n=62), other broad QRS >120ms (n=486), poor quality of the ECG (n=703), missing data of Q wave or TWI (n=29) and those where the STEMI criteria were not fulfilled (n=953) were excluded. The final study population consisted of 7,831 patients.

Study outcomes

The primary outcome was a composite of cardiovascular death, cardiogenic shock, recurrent myocardial infarction or new or worsening New York Heart Association (NYHA) class IV heart failure within one year follow-up. Secondary outcome was all-cause death within one year.

ECG analysis

ST-elevation (STE) measurements were done from the J point and the TP-segment was used as the isoelectric line. We used a modified cut-off point of 0.2 mV for the leads V2 and V3, because the investigators were blinded with respect to the patients' sex and age. A guideline-based cut-off point 0.1 mV in at least two adjacent leads was used in all other leads [14]. STEMI was defined as anterior (V1-V6), inferior (II, III, aVF) or lateral (I, aVL, V5-6) and/or other. In the leads V2 and V3, pathological Q waves were defined as any Q wave ≥0.02 sec in duration or a QS configuration. For all other leads, Q waves ≥0.03 sec in duration and ≥0.1 mV in amplitude were interpreted as pathological if seen in at least two adjacent leads. TWI was defined as a fully negative T wave or a biphasic T wave with ≥0.05 mV negative terminal portion. Patients were divided into four groups based on pathological Q waves and TWI, as shown in Fig. 1.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR) and categorial variables as counts and percentages. To determine differences among groups, ANOVA test and Kruskal-Wallis test were used for normally and non-normally distributed continuous variables, respectively. Chi-square test was used for categorial variables. In the analysis of effects of different Q wave and TWI groups on the risk of primary and secondary outcomes, proportional hazards assumption of the conventional Cox model was first evaluated by Schoenfeld residuals. Because of the violation of proportional hazard assumption, an extended Cox regression model with a time-dependent covariate was implemented, where the introduction of an interaction term of Q wave/TWI group variable and dichotomized time-dependent indicator function allowed varying effects in different follow-up periods. The optimal change point τ for the dichotomized time-dependent indicator was identified by fitting a set of τ values into the model and selecting the one that maximized the log partial likelihood. Hazard ratios (HR) and 95 % confidence intervals (CI) were reported separately for periods before and after change point. Cumulative incidences for primary outcome and all-cause death were explored using Kaplan-Meier curves separately for periods before and after change point. For the multivariable analysis, age, and symptom onset (6-12hrs vs. <6hrs) were forced into the model. In order to achieve a parsimonious model, other pre-specified risk factors or confounding factors including gender, location of MI, current smoking, hypertension, diabetes mellitus, previous MI, previous PCI, proximal lesion (located at least in one of the following: (1) Right coronary artery (RCA) origin, (2) RCA proximal including right ventricle, (3) Left main coronary artery, (4) 3mm after origin of left anterior descending (LAD), (5) Left circumflex proximal, (6) LAD proximal (first 3mm of the proximal LAD)), heart rate, Killip class ≥2, TIMI flow 0 before PCI, thrombus grade (5 vs. <5), time from symptom onset to procedure, elevated troponin and cardiogenic shock were tested for inclusion based on their influence and model fit. Variables with p-value >0.05 were excluded using backwards elimination approach. In addition to the above-mentioned analysis of combined Q waves and TWI, Q waves and TWI were also analyzed as two separate variables in a similar way with the

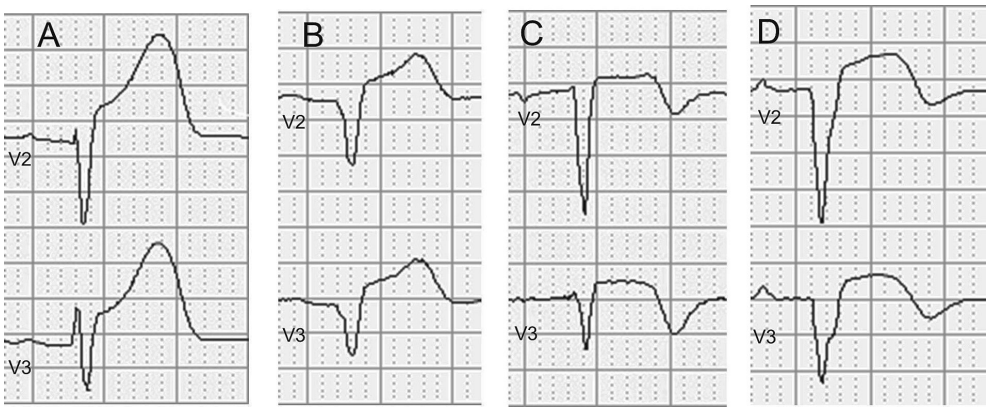

Fig. 1. A: no pathological Q waves and no TWI (Q-TWI-); B: pathological Q wave but no TWI (Q+TWI-); C: no pathological Q wave but TWI (Q-TWI+) and D: both pathological Q wave and TWI present (Q+TWI+).

extended Cox regression model. The effect of routine thrombectomy and PCI alone between different Q wave and TWI groups and Q waves and TWI separately on the risk of primary outcome was assessed by likelihood ratio test of interaction term using unadjusted Cox regression model. A two-sided p-value of <0.05 was considered statistically significant. All analyses were executed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Identification of optimal change point

The optimal change point τ for each model was identified with the method described in statistical analysis section above and ranged between 35 to 45 days depending on the clinical outcomes and whether Q wave and TWI were analyzed jointly or separately. For easy clinical interpretation and presentation, we decided to set the change point to 40 days for all analyses. By short term we refer to cumulative incidence in $\leq$40 days and long term from >40 days to up to 1 year.

Results

Baseline characteristics

The baseline characteristics are shown in Table 1. Patients with the Q-TWI+ pattern were slightly older and were more often females compared with the other groups. There was a trend for higher heart rate and higher blood pressure in patients with the Q+TWI+ pattern. Killip class $\geq$2 was more often seen in patients with the Q+TWI- and Q+TWI+ patterns. Patients with the Q-TWI- pattern more often had inferior MI, while patients with Q+TWI- and Q+TWI+ more often had anterior MI. Patients with the Q-TWI+ and Q+TWI+ patterns were more often diabetic, had higher total CK count and a higher rate of elevated troponin levels. There were no differences among the four groups regarding diagnosis of hypertension, previous MI, previous PCI, peripheral artery disease or current smoking. Patients with the Q+TWI+ pattern had a longer time from symptom onset to hospital arrival and onward to the invasive procedure. Enoxaparin and upfront glycoprotein IIa/IIIb inhibitor therapy were more frequently used in the patients with the Q-TWI- pattern. Higher TIMI thrombus grade and a higher rate of TIMI 0 flow before PCI was seen in patients with the Q+TWI- pattern. Median procedure time did not differ among the groups. Ticagrelor was more often used in patients with the Q-TWI- pattern, while clopidogrel was more frequently used in the other groups. Patients with the Q+TWI- or the Q+TWI+ patterns were more frequently on oral anticoagulants.

Patient outcome in the different Q-wave/TWI categories

Patients with the Q+TWI+ pattern had the highest risk for primary outcome within 40 days compared to patients with the Q-TWI- pattern [33 (10.5%) vs. 221 (4.2%); aHR 2.10; 95% CI, 1.45-3.04; p<0.001]. Patients with the Q+TWI- pattern also had higher risk for primary outcome within 40 days compared to patients with the Q-TWI- pattern [157 (8.2%) vs. 221 (4.2%); aHR 1.78; 95% CI, 1.44-2.20; p<0.001]. There was no statistically significant difference in the risk of primary outcome between the Q-TWI+ and Q-TWI- patients in the 40-day period [21 (5.9%) vs. 221 (4.2%); aHR 1.08; 95% CI, 0.68-1.71; p=0.743]. Beyond 40 days, patients with the Q-TWI+ pattern had a higher risk for primary outcome compared to the patients with the Q-TWI- pattern [15 (4.6%) vs. 101 (2.0%); aHR 1.82; 95% CI, 1.06-3.14; p=0.031]. There was no excess cumulative incidence for primary outcome after 40 days regarding the Q+TWI+ and Q+TWI- groups compared to the patients in the Q-TWI- group. The patients with the Q+TWI+ pattern also had the highest risk for all-cause death within 40 days compared to the patients with the Q-TWI- pattern [22 (7.0%) vs. 83 (1.6%); aHR 3.50; 95% CI, 2.17-5.65; p<0.001]. A higher risk for all-cause death was also seen in the Q+TWI- group compared to the Q-TWI- group in the 40-day time period [71 (3.7%) vs. 83 (1.6%); aHR 1.96; 95% CI, 1.42-2.72;

Table 1
Baseline characteristics.

Characteristic[a]	Q-TWI- (n=5242)	Q+TWI- (n=1922)	Q-TWI+ (n=354)	Q+TWI+ (n=313)	p value[b]
Age (year)	60.6 ± 11.8	60.4 ± 11.6	63.2 ± 12.3	60.9 ± 13.0	<0.001
Age >75 years	636 (12.1)	217 (11.3)	64 (18.1)	49 (15.7)	0.001
Gender (Male)	3985 (76.0)	1576 (82.0)	240 (67.8)	253 (80.8)	<0.001
Heart rate (beats per minute)	74.3 ± 16.9	80.1 ± 17.5	77.1 ± 19.2	83.6 ± 17.5	<0.001
Systolic blood pressure (mmHg)	134.7 ± 26.5	136.5 ± 25.4	136.9 ± 28.7	138.5 ± 28.3	0.006
Diastolic blood pressure (mmHg)	81.7 ± 16.4	84.5 ± 16.5	81.9 ± 16.5	84.8 ± 17.4	<0.001
BMI, kg/m^2	27.8 ± 4.7	27.3 ± 4.3	27.4 ± 4.9	26.7 ± 4.6	<0.001
Killip class ≥2	164 (3.1)	109 (5.7)	12 (3.4)	19 (6.1)	<0.001
Location of MI					<0.001
Anterior	1480 (28.2)	1222 (63.6)	144 (40.7)	202 (64.5)	
Inferior	3494 (66.7)	626 (32.6)	201 (56.8)	101 (32.3)	
Lateral or other	265 (5.1)	72 (3.7)	9 (2.5)	10 (3.2)	
Hypertension	2604 (49.7)	924 (48.1)	193 (54.5)	149 (47.6)	0.131
Diabetes	944 (18.0)	296 (15.4)	78 (22.0)	70 (22.4)	<0.001
Previous MI	433 (8.3)	185 (9.6)	29 (8.2)	31 (9.9)	0.258
Previous PCI	423 (8.1)	157 (8.2)	26 (7.3)	25 (8.0)	0.964
Peripheral arterial disease	108 (2.1)	41 (2.1)	10 (2.8)	10 (3.2)	0.461
Current smoker	2408 (45.9)	891 (46.4)	149 (42.1)	139 (44.4)	0.478
Total CK (U/L)	189.0 (104.0-514.0)	286.0 (133.0-964.0)	343.0 (153.0-936.0)	575.0 (166.0-1634.0)	<0.001
Elevated troponin	2833 (54.0)	1259 (65.5)	251 (70.9)	241 (77.0)	<0.001
Initial PCI procedure					
Onset to Hospital (min)	114.0 (66.0-190.0)	136.0 (80.0-235.0)	162.0 (82.0-300.0)	185.0 (100.0-360.0)	<0.001
Hospital to procedure (min)	48.0 (21.0-85.0)	50.0 (23.0-84.0)	65.0 (28.0-104.0)	67.0 (31.0-101.0)	<0.001
Enoxaparin	453 (8.6)	150 (7.8)	22 (6.2)	12 (3.8)	0.009
Glycoprotein IIb/IIIa inhibitor					
Upfront	1380 (26.3)	477 (24.8)	72 (20.3)	70 (22.4)	0.030
Bailout	766 (14.6)	305 (15.9)	52 (14.7)	55 (17.6)	0.336
Initial TIMI thrombus grade					<0.001
0: no thrombus	135 (2.6)	36 (1.9)	17 (4.8)	9 (2.9)	
1: possible thrombus	278 (5.3)	67 (3.5)	24 (6.8)	16 (5.1)	
2: definitive thrombus, <0.5 x vessel diameter	153 (2.9)	40 (2.1)	11 (3.1)	13 (4.2)	
3: definitive thrombus, 0.5-2.0 x vessel diameter	556 (10.6)	179 (9.3)	47 (13.3)	35 (11.2)	
4: definitive thrombus, >2.0 x vessel diameter	727 (13.9)	210 (10.9)	62 (17.5)	56 (17.9)	

(*continued on next page*)

Table 1 (*continued*)

Characteristic[a]	Q-TWI- (n=5242)	Q+TWI- (n=1922)	Q-TWI+ (n=354)	Q+TWI+ (n=313)	p value[b]
5: total occlusion	3390 (64.7)	1389 (72.3)	193 (54.5)	184 (58.8)	
TIMI 0 flow before PCI	3462 (66.0)	1428 (74.3)	194 (54.8)	202 (64.5)	<0.001
Median PCI procedure time (min)	36.0 (27.0-50.0)	36.0 (26.0-50.0)	38.0 (28.0-54.0)	38.0 (29.0-54.0)	0.062
Clopidogrel	3621 (69.1)	1427 (74.2)	263 (74.3)	225 (71.9)	<0.001
Ticagrelor	1429 (27.3)	422 (22.0)	81 (22.9)	66 (21.1)	<0.001
Oral anticoagulants	249 (4.8)	166 (8.6)	20 (5.6)	22 (7.0)	<0.001

MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Values are given as counts and percentage; mean ± SD or median and interquartile range.

[b] p value is from ANOVA test for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variable, and Chi-square test for categorical variables.

p<0.001]. Similar to the results of primary outcome, there was no additive risk for all-cause death after 40 days in the Q+TWI+ and Q+TWI- groups compared to the Q-TWI- group. There was no statistically significant difference in the risk of all-cause death between the Q-TWI+ and Q-TWI- groups before or after the 40-day time period. The results are shown in Table 2. The cumulative incidences of primary outcome and all-cause death in the time periods ≤40 days and >40 days for the different patient groups are shown in Figs. 2 and 3.

The effect of Q waves and TWI on patient outcome

The baseline characteristics of patients with/without Q waves and with/without TWI are shown in *Supplementary Table 1*. Patients with pathological Q waves in the pre-procedure ECG had a higher risk for primary outcome and all-cause death within 40 days compared to patients with no Q waves [aHR 1.80; 95% CI, 1.48-2.19; p<0.001 and aHR 2.01; 95% CI, 1.50-2.71; p<0.001, respectively] but there was no additive risk after 40 days either in primary outcome or all-cause death. Patients with TWI in the pre-procedure ECG had a higher risk for the primary outcome after 40 days and higher risk for all-cause death in the time period ≤40 days compared to patients with no TWI [aHR 1.63; 95% CI, 1.04-2.55; p=0.033 and aHR 1.65; 95% CI, 1.13-2.41; p=0.010, respectively]. There was no statistically significant difference between patients with TWI and no TWI regarding the risk for primary outcome within 40 days or all-cause death after 40 days. The results are shown in Table 2.

Effect of aspiration thrombectomy

The effect of manual aspiration thrombectomy or PCI alone for the risk of primary outcome within different patient groups are shown in Table 3. The patients with the Q+TWI+ pattern showed a trend towards a lower risk for primary outcome with thrombectomy, but the result was not statistically significant [HR 0.60; 95% CI, 0.31-1.15]. There was no statistically significant interaction between the different patient groups for the effect of treatments on the risk of primary outcome.

Discussion

In this substudy of the TOTAL trial, one of the largest randomized studies of STEMI patients treated invasively, we showed that patients with both Q waves and inverted T waves (Q+TWI+ pattern) in their pre-procedural ECG have an increased risk for the composite endpoint of cardiovascular death, cardiogenic shock, recurrent MI or new or worsening NYHA class IV heart failure and all-cause death compared with other combinations of Q waves and TWI.

Although both pathologic Q waves and TWI were associated with an increased risk for adverse outcome, the effect of Q waves seemed to be short term, while TWI had a more long-term effect. These findings

Table 2
Analysis of the effect of different Q wave and TWI categories and Q waves and TWI separately on the primary outcome and all-cause death during time periods before and after 40 days.

	Period 1: ≤ 40 days			Period 2: > 40 days		
Primary outcome	n/N(%)	aHR (95% CI)[a]	p value	n/N(%)	aHR (95% CI)[a]	p value
Model #1						
Q-TWI-	221/5242 (4.2)	ref	-	101/4970 (2.0)	ref	-
Q+TWI-	157/1922 (8.2)	1.78 (1.44-2.20)	<0.001	34/1746 (1.9)	0.96 (0.65-1.42)	0.838
Q-TWI+	21/354 (5.9)	1.08 (0.68-1.71)	0.743	15/329 (4.6)	1.82 (1.06-3.14)	0.031
Q+TWI+	33/313 (10.5)	2.10 (1.45-3.04)	<0.001	8/277 (2.9)	1.28 (0.62-2.64)	0.504
Model #2						
No Q wave	242/5596 (4.3)	ref	-	116/5299 (2.2)	ref	-
Q wave	190/2235 (8.5)	1.80 (1.48-2.19)	<0.001	42/2023 (2.1)	0.91 (0.63-1.30)	0.600
No TWI	378/7164 (5.3)	ref		135/6716 (2.0)	ref	
TWI	54/667 (8.1)	1.14 (0.85-1.52)	0.392	23/606 (3.8)	1.63 (1.04-2.55)	0.033
All-cause death	n/N(%)	aHR (95% CI)[b]	p value	n/N(%)	aHR (95% CI)[b]	p value
Model #1						
Q-TWI-	83/5242 (1.6)	ref	-	83/5118 (1.6)	ref	-
Q+TWI-	71/1922 (3.7)	1.96 (1.42-2.72)	<0.001	28/1838 (1.5)	0.85 (0.55-1.31)	0.455
Q-TWI+	11/354 (3.1)	1.47 (0.78-2.78)	0.230	12/340 (3.5)	1.65 (0.90-3.03)	0.106
Q+TWI+	22/313 (7.0)	3.50 (2.17-5.65)	<0.001	4/290 (1.4)	0.64 (0.24-1.77)	0.393
Model #2						
No Q wave	94/5596 (1.7)	ref	-	95/5458 (1.7)	ref	-
Q wave	93/2235 (4.2)	2.01 (1.50-2.71)	<0.001	32/2128 (1.5)	0.76 (0.50-1.14)	0.183
No TWI	154/7164 (2.1)	ref		111/6956 (1.6)	ref	
TWI	33/667 (4.9)	1.65 (1.13-2.41)	0.010	16/630 (2.5)	1.31 (0.77-2.22)	0.323

[a] Adjusted for age, symptom onset, gender, diabetes, previous MI, proximal lesion, heart rate, Killip class≥2, cardiogenic shock

[b] Adjusted for age, symptom onset, diabetes, previous MI, previous PCI, proximal lesion, heart rate, Killip class≥2, cardiogenic shock

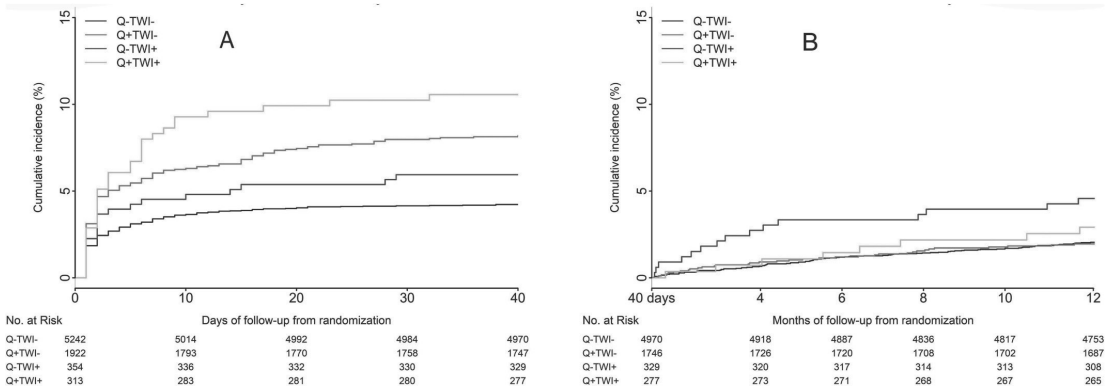

Fig. 2. Kaplan Meier estimate of cumulative incidence of primary outcome for time periods before (panel A) and after (panel B) 40 days.

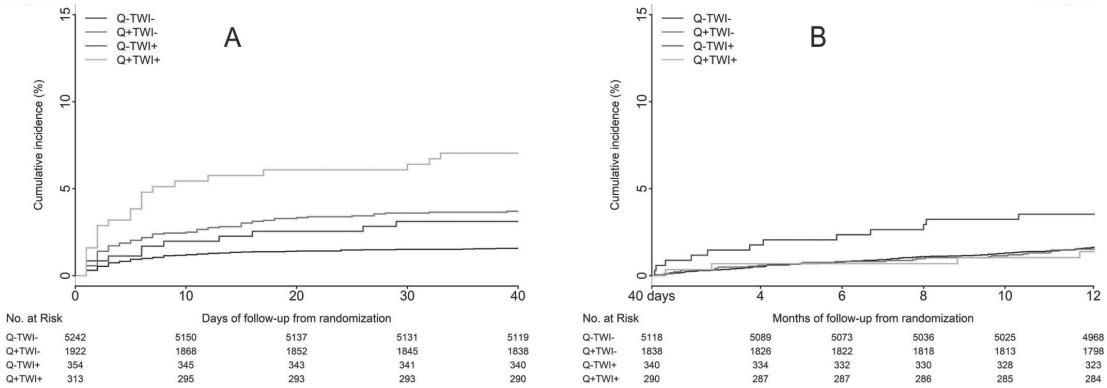

Fig. 3. Kaplan Meier estimate of cumulative incidence of all-cause death for time periods before (panel A) and after (panel B) 40 days.

corroborate those of a previous smaller study [1].

In STEMI patients, pathological Q waves upon admission have been associated with an increased risk for adverse outcome in several previous studies [1–8]. Several pathophysiological mechanisms could provide an explanation for this association. Q waves have been linked to microvascular injury, which, in turn, has been associated with adverse outcome in acute MI [15,16]. Studies have shown that Q waves in patients with acute MI indicate larger infarct size, but not necessarily transmural extension of myocardial injury, and large infarct size is a marker of worse outcome [15,17,18]. In general, anterior infarcts are thought to be larger than inferior infarcts. In our present study, patients with Q waves were more likely to have anterior infarcts, but a higher total CK or troponin level was not explicitly confined to patients with Q waves. A higher TIMI thrombus grade and higher rate of TIMI 0 flow before PCI was also seen in patients with Q waves. Our analysis did take these factors into consideration, showing that they did not affect the outcome of patients with Q waves. Q waves have also been considered as markers of intramyocardial hemorrhage. However, Q waves can be transient, representing myocardial stunning, and they may regress after reperfusion treatment, which is considered as an indicator of improvement in left ventricular ejection fraction [15,17,19,20]. The possible transient nature of Q waves could be one reason for our study findings that Q waves increase the risk of adverse outcome in the early phase but not later on.

TWI in the presenting ECG of STEMI patients has been linked to patency of the infarct-related artery, but also with non-patency, possibly depending on the time from symptom onset. Patients with TWI had worse outcome at least in the late presenters [9,10,21–23]. In our study, TWI was associated with an increased risk for cardiovascular death, cardiogenic shock, recurrent MI or new or worsening NYHA class IV heart failure, but only after 40 days. Interestingly, TWI was associated with higher risk for all-cause death in the early phase, but not after 40 days. One could speculate that this reflects the effect of T wave normalization on the outcome, analogous to transient Q waves. It has been shown that patients with transient TWI or T-wave normalization after reperfusion treatment have better outcome and less extensive myocardial damage compared to patients with persistent TWI after 4 months [24,25]. TWI with early T-wave normalization could be related to a myocardial stunning, while other studies have demonstrated that TWI could be a sign of myocardial edema in patients with non-ST elevation MI and myocarditis [26–28]. We have no definite explanations for these seemingly contradictory findings. Our study included only the pre-procedural ECG, and therefore, no conclusions can be drawn about temporal changes in the T-wave morphology.

Time from symptom onset has been regarded as a key factor for the outcome of patients with STEMI [29–31]. However, some studies have demonstrated that time from symptom onset is not an independent predictor of outcome [3,5]. Furthermore, Q waves and TWI were previously found to be independently predictive of adverse outcome regardless of time from symptom onset, a finding also observed in our

Table 3
Effect of treatments on 1-year primary outcome subgrouped by Q wave and TWI.

	Thrombectomy		PCI alone			
Subgroups	events/ patients	event rate (%)	events/ patients	event rate (%)	HR (95% CI)	p value for interaction[a]
Q-TWI-	162/ 2633	6.2	160/ 2609	6.1	1.00 (0.81-1.25)	0.451
Q+TWI-	97/964	10.1	94/958	9.8	1.03 (0.77-1.37)	
Q-TWI+	20/186	10.8	16/168	9.5	1.13 (0.58-2.18)	
Q+TWI+	14/142	9.9	27/171	15.8	0.60 (0.31-1.15)	
Q wave						
No	182/ 2819	6.5	176/ 2777	6.3	1.02 (0.83-1.25)	0.606
Yes	111/ 1106	10.0	121/ 1129	10.7	0.93 (0.72-1.21)	
TWI						
No	259/ 3597	7.2	254/ 3567	7.1	1.01 (0.85-1.20)	0.343
Yes	34/328	10.4	43/339	12.7	0.80 (0.51-1.26)	

[a] p value for interaction is from likelihood ratio test of interaction term, using unadjusted Cox regression model

study [3,5,10]. While time from symptom onset to hospital arrival and further on to the invasive procedure differed among the patient groups, with the Q+TWI+ patients having the longest delays, Q waves and TWI remained independent predictors of outcome regardless of the time from symptom onset. This implies that different Q and TWI patterns are not simply markers of different temporal stages of the MI disease process, but rather represent different pathophysiological processes associated with acute STEMI.

Routine aspiration thrombectomy was not superior to PCI alone when comparing the different Q wave and TWI groups or when Q waves and TWI were analyzed separately, and therefore, we cannot make recommendations regarding these treatment strategies.

Limitations

Despite the fact that the analyses were adjusted for numerous confounding factors, some unaccounted factors might still have existed and affected our results. Although the TOTAL trial was one of the largest STEMI trials, the numbers of patients in the Q-TWI+ and Q+TWI+ groups were rather small, which could have affected the results via lack of power, when the follow-up was split into two time periods. Some of the patients had deep inverted T waves, while others had a biphasic T wave with only a minor negative terminal portion. Due to the categorical classification of TWI used in this study, we were unable to account for the differences in TWI morphology and thus this may have affected our results.

Conclusions

Our study shows that STEMI patients with both Q waves and TWI in the presenting ECG (Q+TWI+ pattern) have worse outcome than patients with neither in their pre-PCI ECG. Q waves mainly affected short-term outcome, while TWI tended to affect long-term outcome, while both ECG parameters independently predicted adverse outcome. Considering different Q-wave and TWI categories in acute STEMI might be more useful than stratification based on multiple ECG parameters used individually. Conclusive data for tailoring of STEMI treatment based on Q-wave and TWI classification would require prospective studies with randomization according to the ECG changes.

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Disclosures

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CRediT authorship contribution statement

Joonas Leivo: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Funding acquisition. **Eero Anttonen:** Formal analysis, Investigation, Writing – review & editing. **Sanjit S. Jolly:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Vladimír Džavík:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Jyri Koivumäki:** Formal analysis, Investigation, Writing – review & editing. **Minna Tahvanainen:** Formal analysis, Investigation, Writing – review & editing. **Kimmo Koivula:** Formal analysis, Investigation, Writing – review & editing. **Kjell Nikus:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision. **Jia Wang:** Methodology, Formal analysis, Writing – review & editing. **John A. Cairns:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Kari Niemelä:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Markku Eskola:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2023.05.010.

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