The electrocardiographic window of opportunity to treat vs. the different evolving stages of ST-elevation myocardial infarction: correlation with therapeutic approach, coronary anatomy, and outcome in the DANAMI-2 trial

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Aims The aim of the study was to assess two distinct 12-lead electrocardiogram (ECG) patterns and their prognostic value with respect to reperfusion strategy.

Methods and results In a DANAMI-2 substudy (n = 1522), we defined the pre-infarction syndrome (PIS) as ST-elevation accompanied by positive T waves and evolving myocardial infarction (EMI) as pathological Q waves and/or negative T wave. We used a composite of death, clinical re-infarction, or disabling stroke at median 2.7 year follow-up. A higher overall event rate was observed in the EMI group compared with the PIS group [11.4 (9.4–13.9) and 6.9 (6.0–8.0) per 100 person-years, respectively, ratio of the rate (RR) 1.6, \( P < 0.001 \)]. The EMI pattern was independently predictive of adverse outcome in multivariable analysis (hazard ratio 1.52, confidence interval 1.01–2.30, \( P = 0.04 \)). The PIS pattern (n = 952) was associated with lower overall event rate in patients treated with primary percutaneous coronary intervention (PCI) compared with fibrinolytic therapy (FT) [5.5 (4.4–6.9) and 8.5 (7.0–10.4) per 100 person-years, respectively, \( RR = 0.6, P = 0.004 \)]. No significant difference in the outcome between treatment strategies was observed in the EMI group as a whole. However, in patients with anterior EMI without ECG signs of reperfusion, superiority of primary PCI was driven by a 51% reduction in the relative risk of composite endpoint (\( P = 0.008 \)).

Conclusion More detailed ECG analysis, involving also Q- and T-wave morphology, is useful for rapid identification of high-risk patients in whom every effort should be made to transfer for primary PCI, or vice versa, for identifying low-risk patients in whom FT might be an alternative option.

KEYWORDS
Myocardial infarction; Electrocardiogram; Percutaneous coronary intervention; Fibrinolysis; Risk stratification; Prognosis

Introduction

Final infarct size is a major prognostic determinant in acute ST-elevation myocardial infarction (STEMI).\(^1\) Duration of coronary occlusion and efficiency of epicardial and myocardial flow restoration are important determinants of myocardial damage.\(^2\),\(^3\) Primary percutaneous coronary intervention (PCI) has several advantages compared with fibrinolytic therapy (FT), such as superior efficacy in restoring coronary blood flow, making it the preferred strategy for STEMI reperfusion today.\(^4\) However, in a global perspective, most patients are treated in hospitals without 24 h/7 day cardiac catheterization facilities. Building up round-the-clock invasive systems is a big logistic and economic challenge. Hence, it would be crucially important to be able to define low-risk populations that could be treated alternatively with FT in the acute phase. The Thrombolysis in Myocardial Infarction (TIMI) risk score identifies a group of high-risk patients who have a reduced mortality with invasive strategy of primary angioplasty.\(^5\) Differences in treatment delay and in patient characteristics modulate the relative survival advantage for primary PCI over fibrinolysis.\(^6\) The acuteness score has been used as a tool to define the different stages of the evolving myocardial infarction (EMI) process.\(^7\) However, such scores may be unpractical in the setting of rapid decision-making about therapeutic strategies in the acute phase.

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Another alternative to define the stage of the infarct process, the use of distinct electrocardiogram (ECG) patterns, has been described by Sclarovsky. Sudden occlusion of a coronary artery or a major side-branch results within seconds in positive and tall T waves, followed by the elevation of the ST-segment ('injury vector') in the ECG. In patients with acute chest pain, this 'pre-infarction syndrome' (PIS) represents the window of opportunity to treat before irreversible myocardial damage develops. Successful reperfusion results in the normalization of the ST-segment, usually accompanied by T-wave inversion, a marker of an open infarct-related artery with restored myocardial blood flow. The pre-infarction stage may evolve towards MI with or without Q waves (EMI).

The aim of the present study was to investigate the distribution of two distinct ECG patterns, PIS and EMI in the acute infarct process, and the impact of the ECG features on outcomes of patients treated with PCI or FT.

Methods
Study patients
The Danish Trial in Acute Myocardial Infarction-2 (DANAMI-2) randomized 1572 patients, from December 1997 to October 2001, with ST-segment elevation acute MI to either primary PCI or FT with intravenous alteplase. A detailed description of inclusion and exclusion criteria for the DANAMI-2 trial has been reported previously. In this substudy, the primary endpoint was a composite of mortality, clinical infarction, and disabling stroke at 2.7 year [median, inter-quartile range (IQ) 1.9–3.6] follow-up. The patients were entered into the database immediately after randomization. Primary endpoint was at 30 days, and during this period, all end-point data on the patients were entered continuously. After a minimum follow-up period of 2 years, the status on admissions (acute MI and stroke) and death was obtained from various registries. Follow-up information was available for all patients utilizing National Social Security number-based registries. The study complies with the Declaration of Helsinki, and the research protocol was approved by the National Ethics Committee of Denmark. All eligible patients provided written informed consent.

For this substudy, baseline ECGs were available and could be linked to the DANAMI-2 database from 1522 patients. Patients with ECG confounders such as left bundle branch block, left ventricular hypertrophy, pacemaker ECG, and right bundle branch block in association with left anterior hemiblock were excluded. Also, patients with ECG signs of lateral STEMI were not included owing to the small number of cases (n = 23). Finally, 1300 patients with anterior (n = 624) or inferior (n = 676) infarct locations were included in the statistical analyses of the substudy. The patients were divided into two subgroups on the basis of ECG findings: PIS (n = 952) and EMI (n = 348). In addition, the EMI group was graded according to ECG signs of reperfusion. The more specific flow charts in Figure 1 illustrate the ECG subgroups and treatment of the patients.

Figure 1 The flow charts showing the subgroups of the patients defined by the electrocardiogram in the whole study population (A) and in the evolving myocardial infarction group (B). EMI, evolving myocardial infarction; PCI, primary percutaneous coronary intervention.
Electrocardiogram analysis

Randomization ECGs were analysed by three investigators blinded to the clinical data and angiographic findings at the independent core laboratory at Tampere University Hospital. Any disagreement between the investigators was resolved by consensus. The ST-segment was measured manually at the J point with the TP-segment as the iso-electric line. The T wave was considered positive or negative if it was 0.5 mm or more above or below the iso-electric line, measured more than 120 ms after the J point. Pathological Q waves were defined by standard criteria. Anterior MI was defined as ST-elevation ≥2 mm, maximally in at least two contiguous chest leads V1–V6. Inferior MI was defined as ≥1 mm ST-elevation in two or more of the extremity leads II, III, and aVF. In case of concomitant ST-elevation in the precordial leads V1–V3, patients were included into the inferior MI group if the sum of ST-elevation was higher in leads V1–V2 than in leads V2–V3. Patients with ST-elevations (in two or more leads) in leads II, III, and aVF with concomitant ST-elevation in leads V4–V6 but not in leads V1–V3 were classified as inferior MI.

Definitions

The ‘pre-infarction syndrome’ was defined as ST-segment elevation fulfilling the aforementioned criteria for anterior or inferior MI, but without pathological Q waves or inverted T waves in the leads with ST-elevation (Figure 2A).

Evolving MI was defined by ECG signs of myocardial necrosis (pathological Q waves) and/or signs of reperfusion (negative or biphasic T waves). For convenience, we use the term ‘negative T wave’ also for patients with biphasic T waves with a ≥0.5 mm negative terminal portion. No reperfusion was defined as ST-elevation with a positive T wave (Figure 2B). Incomplete reperfusion was defined as ST-elevation with inversion of the T wave (Figure 2C). Complete reperfusion was defined as an iso-electric ST-segment with a completely inverted T wave (Figure 2D).

Statistics

Categorical variables were expressed as numbers of patients or percentages and continuous variables as medians followed by IQ range. Confidence intervals (CIs) were calculated at the 95% significance level. Statistical significance (two-tailed P-value <0.05) was assessed by the χ² test or Fisher’s exact test for categorical variables and the Mann–Whitney test for numerical variables. The event rates were presented per 100 person-years with CIs. The ratios of the rates (RRs) were analysed by Mantel–Haenszel method. Composite endpoint data between ECG subgroups were plotted as Kaplan–Meier curves. Comparison between groups was performed using log-rank statistic. Cox regression analysis was used to test the prognostic significance of baseline and ECG variables concerning composite endpoints at follow-up. Also, hazard ratios were presented. The multivariable analyses were performed by entering the following variables: age ≥75 years, Killip class on admission, heart rate >100 b.p.m., anterior location of infarction, time to treatment >4 h, weight <67 kg, history of diabetes, history of hypertension, smoking status, gender, lipid-lowering medication, aspirin medication, ECG pattern, and treatment group. The effect of ECG pattern on composite endpoint was determined by evaluating the interaction term (ECG pattern-treatment group). Calculations were performed with the SPSS 12.5 statistical package and the Stata 8.2 for Windows.

Results

Of the 1522 patients, 624 (41%) had an anterior STEMI and 676 (44%) an inferior STEMI based on our ECG criteria (Figure 1A). The ECG pattern of PIS was more common than EMI in patients with acute anterior STEMI (59 vs. 41%, respectively). In inferior infarctions, the ECG pattern of EMI was rare (14%).

The baseline data of patients are presented in Table 1. The patients with PIS were younger and more often smokers compared with the patients with EMI. They also had shorter time to randomization and time to reperfusion therapy. The patients with EMI more often had diabetes and angiotensin-converting enzyme inhibitor medication. They also had faster heart rates, higher systolic blood pressure, and lower ejection fraction than patients with PIS. Only very few patients (4%) with anterior MI had other than the left anterior descending artery as the culprit artery according to angiographic findings. In inferior MI, most cases were caused either by right (74%) or left circumflex (17%) coronary artery occlusions.

The event rate for the composite endpoint was higher in EMI than in the PIS group [11.4 (9.4–13.9) and 6.9 (6.0–8.0) per 100 person-years, respectively, RR 1.6, P < 0.001]. The difference was explained with the higher mortality in the EMI group than in the PIS group [8.3 (6.7–10.4) and 3.9 (3.2–4.7) per 100 person-years, respectively, RR 2.1, P < 0.001]. In multivariable analysis, the ECG finding of EMI predicted poor prognosis compared with the ECG finding of PIS. The other variables which provided independent prognostic information in multivariable analysis were age ≥75 years, aspirin treatment, lipid-lowering treatment, anterior MI, and weight <67 kg (Table 2). The interaction term indicated that the ECG pattern was independently predictive (P for interaction 0.167).

In the patients with PIS (n = 952), the event rate of primary composite endpoint was lower in patients treated with primary PCI compared with FT at follow-up [5.5 (4.4–6.9) and 8.5 (7.0–10.4) per 100 person-years, respectively, RR = 0.6, P = 0.004] (Figure 3A). The difference was explained with the lower re-infarction rate in the primary PCI group than in the FT group [3.0 (2.1–4.3) and 6.8 (5.2–8.7) per 100 person-years, respectively, RR 0.5, P < 0.001]. The
number needed to treat with primary PCI to avoid one endpoint event during 2.7-year follow-up was 17 (CI 9–89). There was no statistically significant difference in mortality, clinical re-infarction, or disabling stroke at 2.7-year follow-up between the two treatment arms within patients with EMI (n = 348) (Figure 3B). In the anterior EMI group, however, the patients with no signs of reperfusion on the ECG (n = 139) treated with primary PCI had a better prognosis than the patients treated with FT (Table 3). In this group, the superiority of primary PCI over FT was driven by a 51% reduction in the relative risk of composite endpoint. The number needed to treat with primary PCI in order to avoid one death, clinical re-infarction, or disabling stroke in a 2.7-year period was 5 (CI 3–26). In inferior EMI without ECG signs of reperfusion, the probability of reaching an endpoint was higher with primary PCI than with FT.

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

Discussion

This study adds new interesting data to our knowledge about prognostic and therapeutic differences between STEMI patient groups. It represents the first study to evaluate the clinical significance of two distinct ECG patterns, ST-segment elevation without (PIS) or with (EMI)
pathological Q waves or negative T waves, in a large patient cohort. We found that patients with PIS had better long-term outcome with primary PCI than with FT. Also, patients with anterior evolving STEMI without T-wave inversion, an ECG sign of reperfusion, had better outcome with invasive therapy than with pharmacological reperfusion. Maximal effort should be put to provide immediate invasive treatment for these patient groups. Data from the National Registry of Myocardial Infarction indicate that benefits and limitations of the reperfusion strategy, patient characteristics, and system delays should be considered when a reperfusion strategy for STEMI is selected. Patient age, duration of symptoms, and infarct location significantly modulated how rapidly the survival advantage of primary PCI compared with FT therapy was lost. Our study adds to these findings by showing differences in treatment response to reperfusion therapy with different ECG presentations. When ECG signs of reperfusion were present, FT resulted in a similar long-term outcome as primary PCI both in anterior and inferior STEMI. Our prediction was based solely on the ECG presentations in the acute phase without knowledge of clinical parameters.

When using only traditional ECG parameters, typically ST-segment elevation, patient outcome in the DANAMI-2 trial in different subgroups has favoured primary angioplasty. Regardless of infarct localization, invasive therapy was superior to non-invasive. Also when comparing the prognostic value of the sum of ST-segment elevations within quartiles, the relative benefit of primary PCI was similar. However, Sejersten et al. recently showed that defining grades of ischaemia on the presenting ECG in the DANAMI-2 study enabled the identification of high-risk patient populations with adverse outcome. This together with the results of our study indicates that extension of ECG interpretation beyond traditional ST-segment analysis is important.

In the present study, patients with EMI had about 1 h longer median time delay from symptom onset to randomization and to reperfusion therapy compared with patients with PIS, indicating a later stage of the evolutionary MI process. We found that time to treatment >4 h was not an independent predictor for outcome when ECG pattern indicating the stage of the infarct process was included into the model. Interestingly, neither PCI treatment was independently predictive. Because of the limitations with patient-reported timing of symptom onset, ECG phasing and acuteness scores were developed, and later modified, by Anderson and Wilkins et al. to estimate the extent to which a patient has progressed through the MI process by the time of clinical presentation. The clinical importance of the Anderson–Wilkins (AW) score has been validated, but

| Table 3 | Composite endpoint at 2.7-year follow-up in the patients with evolving myocardial infarction according to electrocardiogram signs of reperfusion |
|---------|----------------------------------|-------------------|------------------|--------|
| ECG pattern | Primary PCI group, n (%) | Fibrinolysis group, n (%) | P-value |
| Anterior EMI | | | |
| No reperfusion, n = 139 | 15 (20) | 25 (39) | 0.008 |
| Incomplete reperfusion, n = 107 | 16 (32) | 15 (26) | 0.67 |
| Inferior EMI | | | |
| No reperfusion, n = 21 | 4 (36) | 0 (0) | 0.04 |
| Incomplete reperfusion, n = 68 | 7 (21) | 11 (32) | 0.31 |

ECG, electrocardiogram; PCI, percutaneous coronary intervention; EMI, evolving myocardial infarction.
for the acuteness score to be clinically useful, it should be an integral component of a commercial automated ECG analysis program. So far, such programs are not universally available. Our results support an alternative approach using simple ECG patterns to divide STEMI patients into clinically relevant categories. Actually, these patterns are distinguished by the same ECG parameters, the Q and T waves, used in the AW scoring system.

Randomized studies of acute STEMI use cut-off points for the amount of ST-elevation for patient inclusion. Changes in the Q and T waves are not considered. According to our results, clinically important information about the pathophysiology and the timing of the ischaemic process may be contained in these ECG parameters. The predictive value of a negative T wave as a marker of reperfusion has no general agreement. However, it has previously been shown that patients with acute anterior MI, in whom ST-segment elevation and positive T waves persist at discharge from the coronary care unit, have higher probability of a non-patent left anterior descending coronary artery compared with patients with an iso-electric ST-segment with negative T waves. Early inversion of the T wave in the leads with ST-elevation has been associated with improved outcome related to an open infarct-related artery, restored myocardial blood flow, re-appearance of the R wave, and better left ventricular function. Although our patients with EMI had ~4 h median time delay to reperfusion therapy, those with inverted T waves showed no significant difference in outcome between mechanical and pharmacological therapy. This may seem contradictory, as the effect of FT is significantly reduced after 3 h delay from symptom onset to treatment. Also in randomized trials such as PRAGUE-2 and CAPTIM, the superiority of primary PCI relative to fibrinolysis was most evident after 2-3 h delay from symptom onset. Appreciating negative T waves in this context as markers of restored epicardial and myocardial blood flow could explain this finding. Studies have shown that the occurrence of reperfusion before PCI is associated with more favourable clinical outcome. Therapeutic advantages of primary PCI might be less obvious in cases with an open infarct-related artery. High-risk patients, such as those with large thrombus burden and increased risk for distal embolization with no re-flow, may outweigh some of the benefits from PCI. Especially when access to primary PCI is limited, FT could be a reasonable alternative in patients presenting with negative T waves associated with ST-elevation.

The role of Q waves in the acute phase of STEMI is less well established than that of the T wave. Classically, the appearance of Q waves has been associated with irreversible myocardial necrosis. In animal studies, early appearance of Q waves may indicate reperfusion in the ischaemic myocardium. A study by Blumenthal et al. indicated that delayed appearance of Q waves was largely due to a lack of circulation in the infarcted area rather than to prolonged survival time. Severe myocardial ischaemia can produce early QRS changes by inducing intramyocardial conduction delays. Raitt et al. found abnormal Q waves in more than half of patients eligible for thrombolytic therapy with symptom duration less than 1 h to the initial ECG recording. The appearance of abnormal Q waves early in the course of acute MI did not lessen the benefit of reduced infarct size after thrombolytic therapy. On the other hand, the presence of Q waves in the initial ECG was an independent predictor of higher 30-day mortality in patients treated with FT in a recent HERO-2 substudy. In our study, EMI (Q waves present in three-fourth) was associated with worse prognosis compared with PIS. In the anterior EMI group without ECG signs of reperfusion, primary PCI resulted in a dramatic 51% reduction in the relative risk of composite endpoint. According to this, patients with anterior STEMI with Q waves, ST-elevation, and positive T waves should have high priority for invasive therapy. The result is in accordance with the 'pathophysiological message' from the ECG—a high probability of an occluded infarct-related artery (ST-elevation with positive T waves), with an extensive area of jeopardized myocardium (anterior localization).

Our study showed a difference in relative distribution of PIS and EMI between anterior and inferior STEMI. EMI was present in only 14% of inferior STEMI patients, compared with 41% in anterior STEMI. This may be related to differences in the electro/pathophysiological process or to differences in the definition of pathological Q waves. Other investigators have found differences in the proportion of initial Q waves in anterior and inferior STEMI. Interestingly, also the AW score faired differently in anterior and inferior STEMI. In our study, patients with inferior EMI without ECG signs of reperfusion had worse outcome with PCI than with fibrinolysis. This may be only a trend because of the small number of patients in this subgroup (n = 21). We cannot, however, rule out harm caused by invasive therapy in relatively low-risk patients.

Study limitations

This study has some limitations. It was not originally planned as part of the DANAMI-2 study. As the ECG investigators were totally blinded to angiographic findings and clinical data of the patients and the number of patients was large, the post hoc nature of the study should not have significant impact on the results. Data on TIMI perfusion grade would have improved the strength of the comparison between ECG changes and possible pathophysiological mechanisms. Our definition of Q waves did not differ between reperfusion- and necrosis-related Q waves.

Conclusions

We re-evaluated the prognostic significance of two distinct ECG patterns in the modern era of acute STEMI treatment by including changes in the Q and T waves. We found that patients with acute anterior or inferior STEMI without Q waves and with positive T waves and those with anterior MI with Q waves, ST-elevation, and positive T waves had better long-term outcome with primary PCI than with FT. If T-wave inversion was present, FT resulted in similar long-term outcome as primary PCI both in anterior and inferior STEMI. Because of the post hoc nature of this study, the results should be assessed with caution. However, this finding merits prospective testing.

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