Journal of Electrocardiology 51 (2018) 598–606

Contents lists available at ScienceDirect

Journal of Electrocardiology

journal homepage: www.jecgonline.com

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

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

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

ARTICLE INFO

Keywords:
ST-elevation myocardial infarction
Myocardial ischemia
Grade of ischemia
Electrocardiography
Prognosis
Mortality

ABSTRACT

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

Introduction

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

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

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

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

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

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

https://doi.org/10.1016/j.jelectrocard.2018.03.014
0022-0736/

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

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

Material and methods

Study population

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

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

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

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

Acute chest pain/discomfort and

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

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

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

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

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

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

ECG analysis

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

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

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

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

Statistical analysis

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

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

Results

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

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

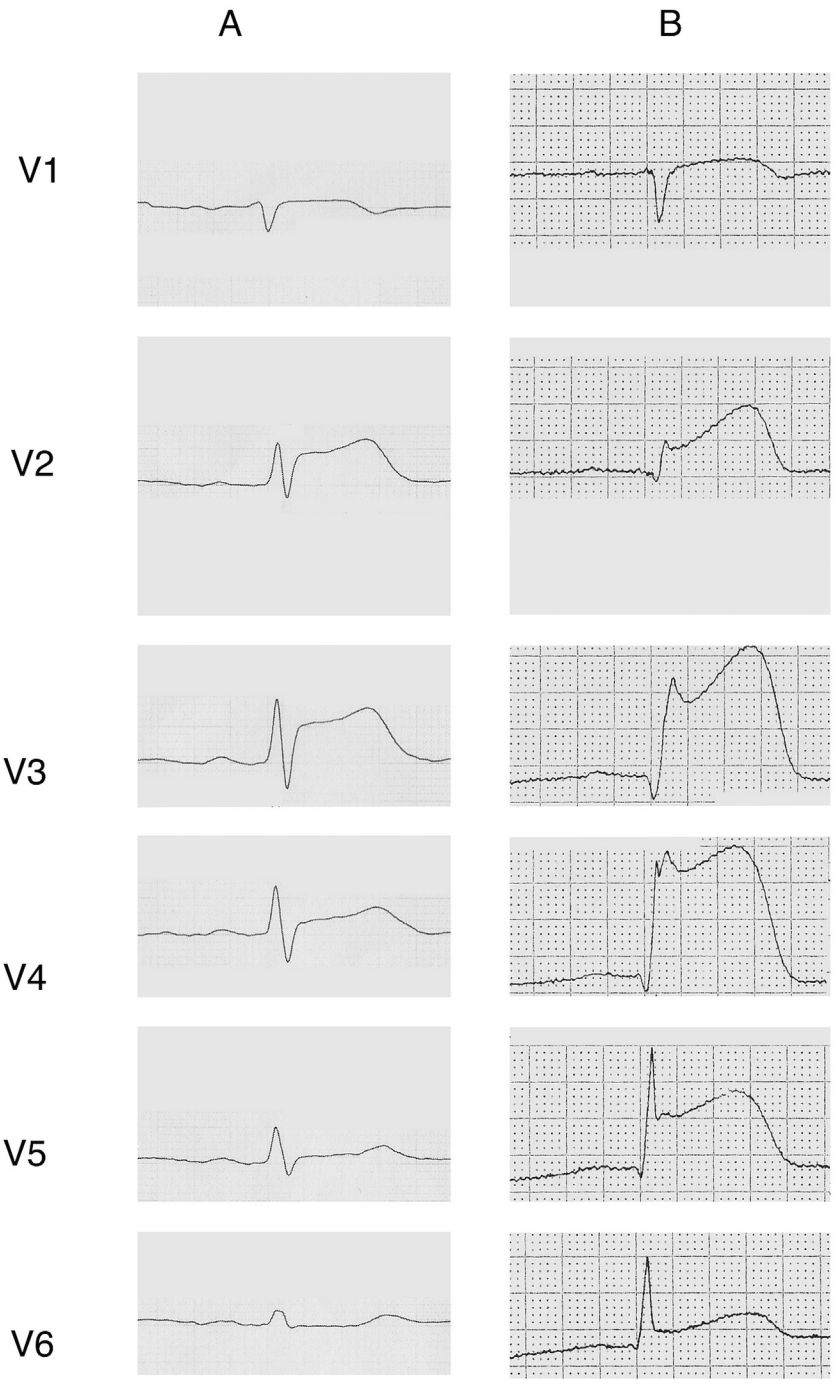

Fig. 1. Grade 2 ischemia (Panel A) and grade 3 ischemia (Panel B) in anterior STEMI (50 mm/s). In an rS type complex (typically V1–V3), G3I is shown as rising of S-wave above baseline.

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

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

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

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

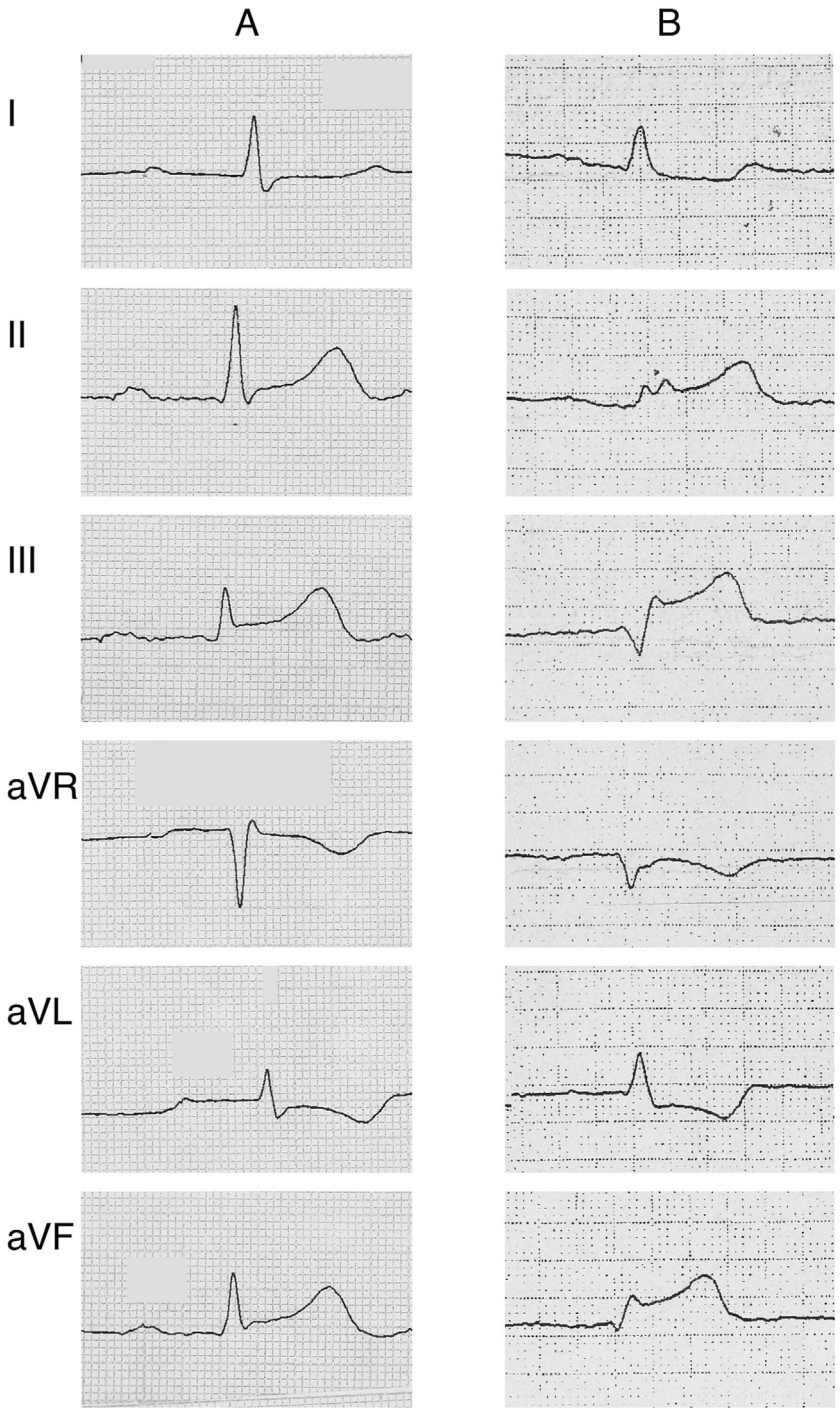

Fig. 2. Grade 2 ischemia (Panel A) and Grade 3 ischemia (Panel B) in inferior STEMI (50 mm/s). In a qR type complex, G3I is shown as ST-elevation >50% of the height of the R-wave.

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

Discussion

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

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

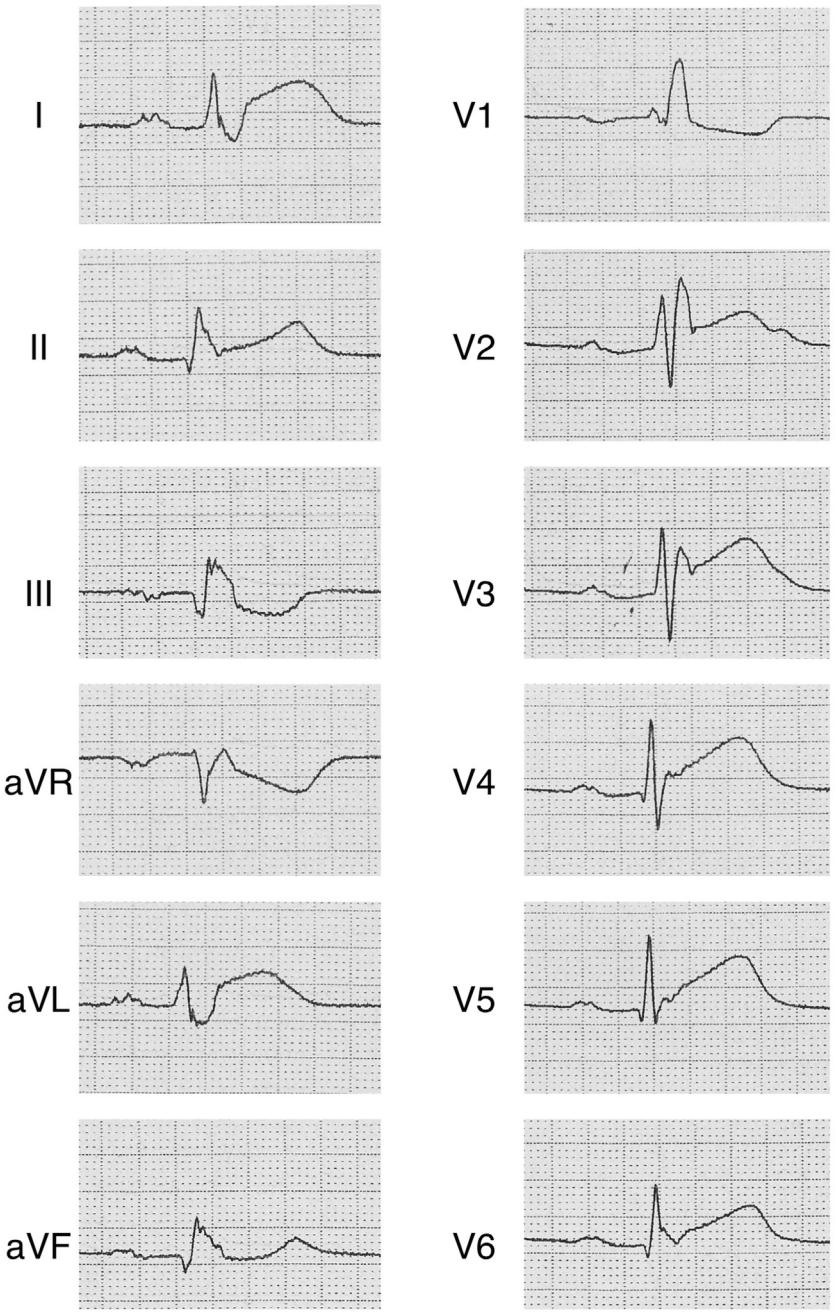

Fig. 3. An example of a patient in the "No grade" group. Anterior STEMI with QRS > 120 ms due to right bundle branch block (50 mm/s).

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

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

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

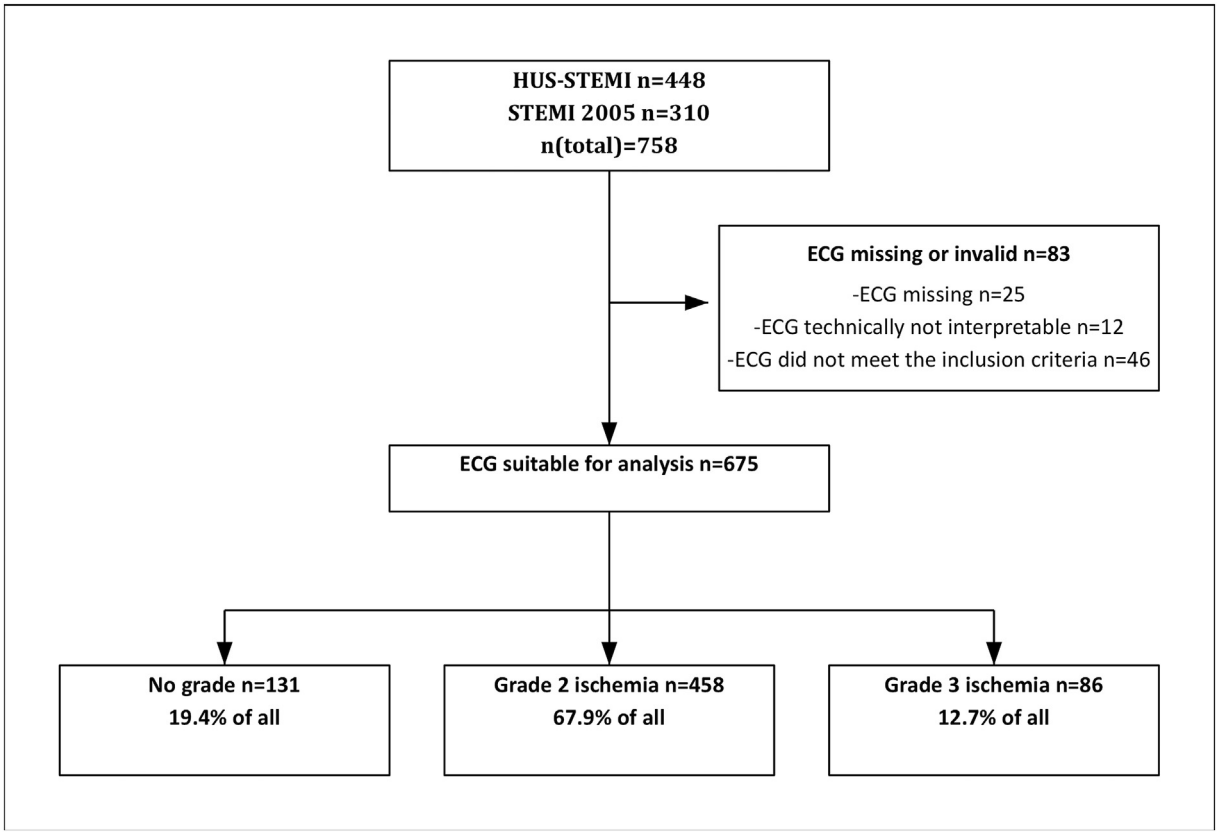

Fig. 4. Number of patients included in the groups No grade, Grade 2 ischemia and Grade 3 ischemia.

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

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

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

Table 2
Outcome based on the grade of ischemia.

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

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

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

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

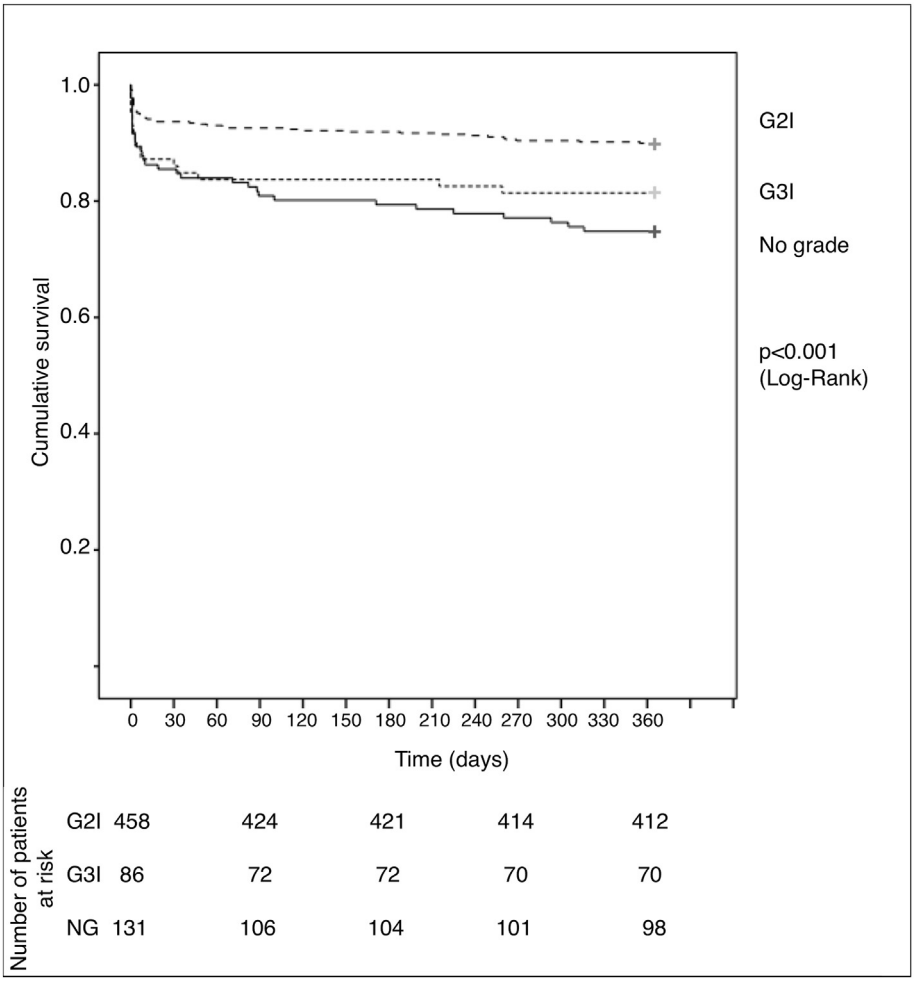

Fig. 5. Kaplan-Meier curve showing the 1-year survival of the patients with NG, G2I and G3I.

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

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

For abbreviations, see Table 2.

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

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

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

Conclusion

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

Limitations

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

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

Funding

This study was supported by grants from the Finnish Cultural Foundation, Special Governmental Subsidy, Finnish Medical Foundation and Viipuri Tuberculosis Foundation.

Declaration of interest

None.

Acknowledgments

The study was supported by grants from the Finnish Cultural Foundation, Special Governmental Subsidy, Finnish Medical Foundation and Viipuri Tuberculosis Foundation. The authors would like to thank all the investigators of the HUS-STEMI and STEMI 2005 studies and study assistants Johanna Muhonen and Hanna Javas-Viikilä.

References

[1] Sclarovsky S, Mager A, Kusniec J, Rechavia E, Sagie A, Bassevich R, et al. Electrocardiographic classification of acute myocardial ischemia. Isr J Med Sci 1990;26:525–31.
[2] Billgren T, Birnbaum Y, Sgarbossa EB, Sejersten M, Hill NE, Engblom H, et al. Refinement and interobserver agreement for the electrocardiographic Sclarovsky-Birnbaum Ischemia Grading System. J Electrocardiol 2004;37:149–56.
[3] Buber J, Gilutz H, Birnbaum Y, Friger M, Ilia R, Zahger D. Grade 3 ischemia on admission and absence of prior beta-blockade predict failure of ST resolution following thrombolysis for anterior myocardial infarction. Int J Cardiol 2005;104:131–7.
[4] Sejersten M, Birnbaum Y, Ripa RS, Maynard C, Wagner GS, Clemmensen P, et al. Influences of electrocardiographic ischaemia grades and symptom duration on outcomes in patients with acute myocardial infarction treated with thrombolysis versus primary percutaneous coronary intervention: results from the DANAMI-2 trial. Heart 2006;92:1577–82.
[5] Birnbaum Y, Goodman S, Barr A, Gates KB, Barbash GI, Battler A, et al. Comparison of primary coronary angioplasty versus thrombolysis in patients with ST-segment elevation acute myocardial infarction and grade II and grade III myocardial ischemia on the enrollment electrocardiogram. Am J Cardiol 2001;88:842–7.

[6] Birnbaum Y, Kloner RA, Sclarovsky S, Cannon CP, McCabe CH, Davis VG, et al. Distortion of the terminal portion of the QRS on the admission electrocardiogram in acute myocardial infarction and correlation with infarct size and long-term prognosis (Thrombolysis in Myocardial Infarction 4 Trial). Am J Cardiol 1996;78:396–403.
[7] Ringborn M, Birnbaum Y, Nielsen SS, Kaltoft AK, Botker HE, Pahlm O, et al. Prehospital evaluation of electrocardiographic grade 3 ischemia predicts infarct progression and final infarct size in ST elevation myocardial infarction patients treated with primary percutaneous coronary intervention. J Electrocardiol 2014;47:556–65.
[8] Rommel KP, Badarnih H, Desch S, Gutberlet M, Schuler G, Thiele H, et al. QRS complex distortion (Grade 3 ischaemia) as a predictor of myocardial damage assessed by cardiac magnetic resonance imaging and clinical prognosis in patients with ST-elevation myocardial infarction. Eur Heart J Cardiovasc Imaging 2016;17:194–202.
[9] Kurt M, Karakas MF, Buyukkaya E, Akcay AB, Sen N. Relation of angiographic thrombus burden with electrocardiographic grade III ischemia in patients with ST-segment elevation myocardial infarction. Clin Appl Thromb Hemost 2014;20:31–6.
[10] Billgren T, Maynard C, Christian TF, Rahman MA, Saeed M, Hammill SC, et al. Grade 3 ischemia on the admission electrocardiogram predicts rapid progression of necrosis over time and less myocardial salvage by primary angioplasty. J Electrocardiol 2005;38:187–94.
[11] Tamura A, Nagase K, Watanabe T, Nasu M. Relationship between terminal QRS distortion on the admission electrocardiogram and the time course of left ventricular wall motion in anterior wall acute myocardial infarction. Jpn Circ J 2001;65:63–6.
[12] Birnbaum Y, Criger DA, Wagner GS, Strasberg B, Mager A, Gates K, et al. Prediction of the extent and severity of left ventricular dysfunction in anterior acute myocardial infarction by the admission electrocardiogram. Am Heart J 2001;141:915–24.
[13] Wong CK, Stewart RA, Gao W, French JK, Raffel C, White HD. Prognostic differences between different types of bundle branch block during the early phase of acute myocardial infarction: insights from the Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial. Eur Heart J 2006;27:21–8.
[14] Herz I, Birnbaum Y, Zlotikamien B, Strasberg B, Sclarovsky S, Chetrit A, et al. The prognostic implications of negative T waves in the leads with ST segment elevation on admission in acute myocardial infarction. Cardiology 1999;92:121–7.
[15] Nikus KEM, Kotila M, Korpilahti K, Kettunen R, Nieminen V, Verho K, et al. English summary: incidence and treatment of ST-elevation myocardial infarction in four hospital districts: stemi-2005 study. Finnish Medical Journal 2008;63:3987–93.
[16] Viikila J, Lilleberg J, Tierala I, Syvanne M, Kupari M, Salomaa V, et al. Outcome up to one year following different reperfusion strategies in acute ST-segment elevation myocardial infarction: the Helsinki-Uusimaa Hospital District registry of ST-Elevation Acute Myocardial Infarction (HUS-STEMI). Eur Heart J Acute Cardiovasc Care 2013;2:371–8.
[17] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551–67.
[18] Birnbaum Y, Herz I, Sclarovsky S, Zlotikamien B, Chetrit A, Olmer L, et al. Prognostic significance of the admission electrocardiogram in acute myocardial infarction. J Am Coll Cardiol 1996;27:1128–32.
[19] Shen AY, Wang X, Doris J, Moore N. Proportion of patients in a congestive heart failure care management program meeting criteria for cardiac resynchronization therapy. Am J Cardiol 2004;94:673–6.
[20] Lemmert ME, de Vreede-Swagemakers JJ, Eurlings LW, Kalb L, Crijns HJ, Wellens HJ, et al. Electrocardiographic predictors of out-of-hospital sudden cardiac arrest in patients with coronary artery disease. Am J Cardiol 2012;109:1278–82.
[21] Eskola MJ, Holmvang L, Nikus KC, Sclarovsky S, Tilsted HH, Huhtala H, et al. The electrocardiographic window of opportunity to treat vs. the different evolving stages of ST-elevation myocardial infarction: correlation with therapeutic approach, coronary anatomy, and outcome in the DANAMI-2 trial. Eur Heart J 2007;28:2985–91.
[22] Shimada YJ, Po JR, Kanei Y, Schweitzer P. Prognostic impact of terminal T wave inversions on presentation in patients with ST-elevation myocardial infarction undergoing urgent percutaneous coronary intervention. J Electrocardiol 2013;46:2–7.
[23] Zalenski RJ, Grzybowski M, Ross MA, Blaustein N, Bock B. ECG scores for a triage of patients with acute myocardial infarction transported by the emergency medical system. J Electrocardiol 2000;33(Suppl):245–9.
[24] Lee CW, Hong MK, Yang HS, Choi SW, Kim JJ, Park SW, et al. Determinants and prognostic implications of terminal QRS complex distortion in patients treated with primary angioplasty for acute myocardial infarction. Am J Cardiol 2001;88(3):210.
[25] Garcia-Rubira JC, Garcia-Borbolla R, Nunez-Gil I, Manzano MC, Garcia-Romero MM, Fernandez-Ortiz A, et al. Distortion of the terminal portion of the QRS is predictor of shock after primary percutaneous coronary intervention for acute myocardial infarction. Int J Cardiol 2008;130:241–5.