

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

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Received 24 November 2014; accepted after revision 2 May 2015; online publish-ahead-of-print 9 June 2015

Aims

Distortion of the terminal portion of the QRS complex (so-called Grade 3 ischaemia, G3I) has been associated with adverse outcomes in ST-elevation myocardial infarction (STEMI) populations. However, the correlation of G3I with infarct size and microvascular injury as defined by cardiac magnetic resonance (CMR) is not well defined. Aim of this study was to assess the relation of G3I with myocardial damage as assessed by CMR and clinical outcomes in STEMI patients.

Methods and results

We analysed the ECGs of 572 consecutive STEMI patients regarding the presence or absence of G3I. CMR was performed within 1 week after infarction for comprehensive assessment of myocardial damage using a standardized protocol. The primary clinical endpoint was major adverse cardiac events (MACE) within 12 months after infarction. G3I was present in 186 (32%) patients. The presence of G3I was associated with larger infarct size ($P = 0.01$), the presence of late microvascular obstruction ($P = 0.05$), the presence of intramyocardial haemorrhage ($P = 0.04$), and impaired myocardial salvage ($P = 0.01$). G3I was associated with a higher incidence of MACE ($P = 0.01$) and was identified as an independent predictor of MACE in Cox regression analysis (HR 2.19; 95% CI 1.10 to 4.38, $P = 0.03$).

Conclusion

This largest study to date correlating G3I on the admission ECG with CMR markers of myocardial damage demonstrates that G3I is significantly associated with infarct size, impaired myocardial salvage, and reperfusion injury in a reperfused STEMI population. Moreover, G3I was independently associated with MACE.

ClinicalTrials.gov NCT00712101.

Keywords

myocardial infarction • prognosis • electrocardiogram • cardiac magnetic resonance

Introduction

Numerous studies have convincingly demonstrated that ST-segment analysis of a 12-lead electrocardiogram (ECG) in patients with ST-elevation myocardial infarction (STEMI) can be used to predict clinical outcomes and myocardial injury after STEMI.^{1–3} Most of these

ECG parameters for risk and prognosis assessment require the comparison of pre- and post-reperfusion ECGs [e.g. analysis of ST-segment resolution (STR)].² Changes in the terminal portion of the QRS complex (G3I) in the pre-treatment ECG have also been shown to be associated with adverse outcome.^{4,5} Originally Birnbaum et al.⁶ reported three grades of ischaemia in patients

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with acute coronary syndrome according to their ECG pattern on admission (Grade 1 ischaemia: peaked T-waves in the involved leads without ST-elevation, Grade 2 ischaemia: ST-elevation without QRS distortion, and Grade 3 ischaemia: ST-elevation and distortion of the terminal QRS complex, G3I).

It has been speculated that the ECG pattern of G3I occurs because of ischaemia affecting the Purkinje fibres of the conduction system, which are less vulnerable to ischaemia than the surrounding myocardium.⁷ Consequently, these depolarization changes are considered to be caused by more severe and prolonged myocardial ischaemia. Indeed, in clinical studies, G3I has been shown to predict incomplete epicardial and microvascular reperfusion as demonstrated by an impaired thrombolysis in myocardial infarction (TIMI)-flow 3 and lower degree of STR. Moreover, patients with G3I had larger infarcts, a higher risk of reinfarction, as well as increased short- and long-term mortality rates.^{4,5,8–11} However, most of these studies share important limitations: (i) they preceded currently guideline recommended clinical practice with routine use of stents and optimal antiplatelet therapy, (ii) they were conducted retrospectively, (iii) they examined rather small and highly selected cohorts, and (iv) infarct characteristics were indirectly measured by biomarkers.

Meanwhile, cardiac magnetic resonance imaging (CMR) has emerged as the reference method for comprehensive assessment of myocardial injury after STEMI. Infarct size (IS), myocardial salvage, microvascular obstruction (MVO), and intramyocardial haemorrhage can be adequately and robustly visualized within one scan after infarction.^{12,13} The relation of G3I with markers of myocardial damage assessed by CMR, however, is not well defined.

Aim of this study was, therefore, to evaluate the relation between the presence of G3I on the pre-hospital ECG with microvascular injury, IS, and left ventricular (LV) function assessed by CMR and with clinical outcomes in patients with reperfused STEMI in the contemporary era.

Methods

Patients and study design

The present analysis was predefined and prospectively conducted as a part of the abciximab intracoronary vs. intravenously drug application in ST-elevation myocardial infarction (AIDA STEMI) trial. The design and results of the study have been published elsewhere.^{14,15} In brief, AIDA STEMI was a randomized, open-label, multicentre trial. Patients with STEMI and symptom duration <12 h were randomly assigned at a 1:1 ratio to intracoronary or intravenous abciximab bolus (0.25 mg/kg bodyweight) during primary percutaneous coronary intervention (PCI) with a subsequent 12-h dose-adjusted intravenous infusion. A total of 2065 patients were enrolled at 22 sites in Germany. The primary endpoint was a composite of all-cause mortality, recurrent infarction, or readmission for new congestive heart failure (MACE) within 90 days of randomization.

As part of the ECG/CMR sub-study, 795 consecutive patients were enrolled at eight sites.¹³ Only subjects undergoing primary PCI and CMR assessment who had an evaluable pre-hospital 12-lead ECG ($n = 593$) were eligible for study inclusion (Figure 1).

ECG analysis

A standard 12-lead ECG was recorded at baseline (first diagnostic ECG, i.e. pre-hospital ECG) and 90 min after PCI according to the AIDA STEMI main protocol. ECGs were analysed centrally in the ECG core laboratory at the University of Leipzig—Heart Center (Leipzig, Germany) by two observers (K.P.R. and H.B.) blinded to patients' characteristics, CMR study data, and clinical outcomes. The presence of G3I was defined as (i) complete loss of S waves in two adjacent leads with typical Rs configuration (i.e. V1–V3), or (ii) ST-J point to R wave amplitude ratio >0.5 in other leads with qR configuration, as reported previously.⁶

ST-segment elevation (STE) was measured 20 ms after the J point to the nearest 0.05 mV. STR and single lead ST-segment resolution (SL-STR) were calculated as described previously.^{2,16} Patients with left bundle branch block ($n = 6$) were excluded. Furthermore, patients presenting with negative T-waves in the leads with STE were not included ($n = 15$) (Figure 1).

CMR analysis

Protocol specified CMR acquisition on Days 1–4 after the index event was performed for the assessment of myocardial salvage, IS, presence and extent of MVO, LV ejection fraction, and LV volumes. The detailed scan protocol on a clinical 1.5- or 3.0-T CMR scanner was described previously.¹⁵ CMR images were evaluated at the CMR core laboratory at the University of Leipzig—Heart Center using certified CMR evaluation software (cmr42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Assessment was performed by observers blinded to patients' characteristics, ECG interpretations, and clinical outcomes.

IS, area at risk (AAR), and MVO were expressed as a percentage of LV volume. Salvaged myocardium was quantified as the difference between the volume of increased T_2 -signal (AAR) and the volume of delayed enhancement (IS) and consequently expressed as myocardial salvage index (MSI), as previously described.¹³ The presence and extent of hypointense infarct cores as indicator of intramyocardial haemorrhage (IMH) were defined as dark area in the centre of the AAR/oedema having a mean signal intensity of at least 2 standard deviations below the signal intensity of the periphery of the AAR, as previously described.¹⁷

Clinical endpoints

The primary endpoint was the occurrence of MACE defined as a composite of death, re-infarction, and new congestive heart failure (CHF) within 12 months after infarction. Re-infarction and new CHF were defined as described previously.^{13–15}

Statistical analysis

Data for continuous variables are presented as medians with interquartile range (IQR). Categorical variables are presented as frequencies and percentages. Comparisons within the groups were made using χ^2 tests for categorical variables and Kruskal–Wallis non-parametric tests for continuous variables.

Univariate and stepwise multivariate logistic regression analyses were performed to identify predictors of G3I. Stepwise multivariate regression was performed using only variables with a P -value of <0.05 in univariate regression analyses. For univariate analyses, all listed baseline characteristics, procedural data, randomization group in the overall AIDA STEMI trial and CMR parameters were investigated.

Kaplan–Meier survival estimates were used to plot the time to first occurrence of the composite of death, CHF, or re-infarction between groups at 12 months. Differences were tested with log-rank tests.

The adjusted associations between G3I and 12-month clinical outcomes were examined using univariate and stepwise multivariate Cox

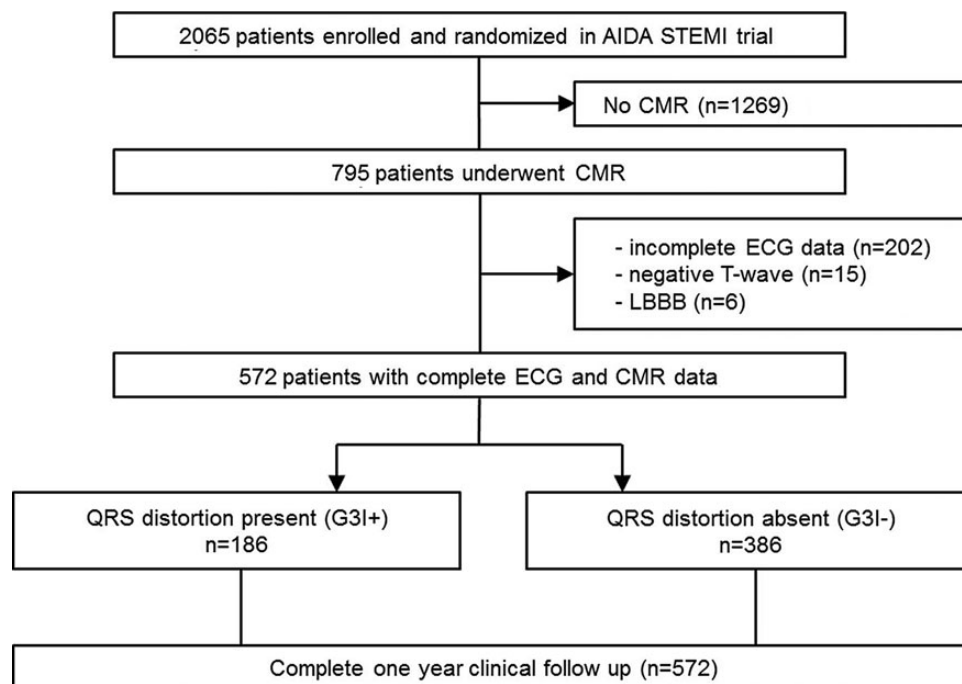


Figure 1 Study profile. AIDA STEMI, abciximab intracoronary vs. intravenously drug application in ST elevation myocardial infarction; CMR, cardiac magnetic resonance; ECG, electrocardiogram; LBBB, left bundle branch block.

proportional hazards regression models, including characteristics at randomization, procedural data, CMR measurements and presences of G3I as covariates. Multivariable Cox regression was performed using only variables with a probability value of <0.05 in univariable Cox regression analyses.

The incremental additive information associated with the presence of G3I and IS, MVO and LV-EF over other established clinical prognostic parameters (TIMI risk score) was assessed using c-statistics.¹⁸ C-statistic results were compared using the non-parametric method previously described by De Long et al.¹⁹

A two-tailed P -value of <0.05 was considered as statistically significant. SPSS version 20.0 was used for statistical analyses.

Results

Suitable pre-hospital ECGs for QRS distortion analysis and CMR exams were present in 572 patients (Figure 1). G3I was present in 186 (32%) patients, whereas 386 patients (68%) did not show distortion of the terminal QRS complex.

Baseline characteristics of the total population and by groups are presented in Table 1. Patients presenting with G3I had significantly more often inferior infarctions ($P = 0.003$), more often complete occlusion of the culprit artery (TIMI-flow 0 before PCI; $P < 0.001$) and a shorter symptom-to-hospital admission time with comparable door-to-balloon times ($P = 0.94$). No significant differences were observed in the frequencies of the presence of diabetes mellitus, previous myocardial infarction, male sex, number of diseased vessels, or age between groups.

CMR results revealed an association of G3I with myocardial damage as shown in Table 2 and Figure 2. Patients with G3I developed

larger infarcts, more pronounced late MVO, a higher frequency of the presence of IMH, and a lower MSI. The AAR and the LV ejection fraction did not differ significantly between groups.

Limiting these analyses to patients with successful PCI defined as TIMI-flow Grade 3 after PCI did not weaken these relationships considerably (data not shown).

Significant predictors of G3I are displayed in Table 3. Inferior infarction ($P = 0.002$) and CMR-derived IS ($P = 0.003$) emerged as independent predictors of distortion of the terminal QRS complex.

The amount of STR and SL-STR did not differ between patients with or without G3I (64%; IQR 37–85 vs. 62%; IQR 31–81, $P = 0.24$ and 75%; IQR 50–93 vs. 75%; IQR 50–93, $P = 0.96$, respectively), although absolute ST-elevation was higher in the G3I group (STE: 1.15 mV; IQR 0.70–1.65 vs. 0.9 mV; IQR 0.55–1.35, $P < 0.001$ and maximum single lead STE: 0.40 mV; IQR 0.25–0.55 vs. 0.30 mV; IQR 0.20–0.40, $P < 0.001$).

Clinical outcome

At 12-month follow-up, patients with G3I experienced significantly more re-infarctions [5.5 vs. 1.8%, $P = 0.02$; Hazard ratio (HR) 3.01, 95% CI 1.18–8.12, $P = 0.02$] (Table 4). In addition, rates of new CHF (3.8 vs. 1.8%, $P = 0.15$; HR 2.14, 95% CI 0.75–6.10, $P = 0.15$) and death (3.3 vs. 2.1%, $P = 0.36$, HR 1.64, 95% CI 0.57–4.72, $P = 0.36$) were numerically higher in the G3I group, although not statistically significant. Consequently, the presence of G3I showed a significant association with MACE at 12 months (12.3 vs. 5.7%, $P = 0.01$; HR 2.27, 95% CI 1.19–4.32, $P = 0.01$) and generated a graded stratification for MACE- and re-infarction-free survival ($P = 0.01$ and $P = 0.02$, respectively) (Figure 3).

Table 1 Patient characteristics

Variable	Total study cohort, n = 572	QRS distortion present (G3I+), n = 186	QRS distortion absent (G3I-), n = 386	P-value
Age (years)	61 (50–71)	62 (51–71)	60 (50–70)	0.21
Male sex: n (%)	442/572 (77)	148/186 (80)	294/386 (76)	0.39
Cardiovascular risk factors: n (%)				
Current smoking	245/519 (47)	79/165 (48)	166/354 (47)	0.83
Hypertension	384/569 (68)	124/186 (67)	260/383 (67)	0.77
Hypercholesterolaemia	220/566 (40)	63/184 (34)	157/382 (41)	0.12
Diabetes mellitus	111/569 (20)	36/186 (19)	75/383 (19)	0.95
BMI (kg/m ²)	27.2 (24.8–30.4)	27.7 (25.0–30.3)	27.1 (24.7–30.5)	0.60
Previous infarction, n (%)	33/571 (6)	10/186 (5)	23/385 (6)	0.77
Anterior infarction, n (%)	269/561 (48)	71/182 (39)	198/379 (52)	0.003
Times (min)				
Symptom onset to PCI hospital admission	179 (108–295)	155 (104–246)	186 (110–319)	0.05
Door-to-balloon time	29 (22–42)	29 (22–41)	30 (22–40)	0.94
Killip-class on admission, n (%)				0.09
1	505/572 (88)	165/186 (89)	340/386 (88)	0.83
2	46/572 (8)	10/186 (5)	36/386 (9)	0.10
3	10/572 (2)	5/186 (3)	5/386 (1)	0.23
4	11/572 (2)	6/186 (3)	5/386 (1)	0.12
TIMI risk score	3 (2–5)	3 (2–5)	3 (2–5)	0.17
Number of diseased vessels, n (%)				0.89
1	298/572 (52)	96/186 (52)	202/386 (52)	0.87
2	173/572 (30)	58/186 (31)	115/386 (30)	0.69
3	101/572 (18)	32/186 (17)	69/386 (18)	0.79
Infarct-related artery, n (%)				0.10
Left anterior descending	248/572 (43)	62/186 (33)	186/386 (48)	0.001
Left circumflex	65/572 (11)	23/186 (12)	42/386 (11)	0.60
Right coronary artery	253/572 (44)	100/186 (54)	153/386 (39)	0.001
Left main	4/572 (1)	1/186 (1)	3/386 (1)	0.75
Bypass graft	2/572 (<1)	0/186 (0)	2/386 (1)	0.33
TIMI flow before PCI, n (%)				<0.001
TIMI flow 0	320/572 (56)	126/186 (68)	194/386 (50)	<0.001
TIMI flow I	73/572 (13)	19/186 (10)	54/386 (14)	0.23
TIMI flow II	93/572 (16)	13/186 (7)	80/386 (21)	<0.001
TIMI flow III	86/572 (15)	28/186 (15)	58/386 (15)	0.99
Thrombectomy, n (%)	134/572 (23)	44/186 (24)	90/386 (23)	0.93
TIMI flow post-PCI, n (%)				0.57
TIMI flow 0	8/571 (1)	2/185 (1)	6/386 (2)	0.65
TIMI flow I	12/571 (2)	6/185 (3)	6/386 (3)	0.19
TIMI flow II	41/571 (7)	14/185 (8)	27/386 (7)	0.80
TIMI flow III	510/571 (89)	163/185 (88)	347/386 (90)	0.52
Intra-aortic balloon pump, n (%)	24/572 (4)	10/186 (5)	14/386 (4)	0.33
Concomitant medications, n (%)				
β-blockers	549/571 (96)	180/186 (97)	369/385 (96)	0.58
ACE-inhibitors/ARB	542/571 (95)	174/186 (94)	368/385 (96)	0.30
Aspirin	572/572 (100)	186/186 (100)	386/386 (100)	NS
Clopidogrel, prasugrel, or both	572/572 (100)	186/186 (100)	386/386 (100)	NS
Statins	551/571 (97)	179/186 (96)	372/385 (97)	0.82

Continued

Table 1 Continued

Variable	Total study cohort, <i>n</i> = 572	QRS distortion present (G3I+), <i>n</i> = 186	QRS distortion absent (G3I-), <i>n</i> = 386	P-value
Aldosterone antagonist	63/571 (11)	22/186 (12)	41/385 (11)	0.67
Gp-IIb/IIIa-inhibitor (abciximab)	539/572 (94)	175/186 (94)	364/386 (94)	0.94
I.c. abciximab administration	282/572 (49)	91/186 (49)	191/386 (50)	0.90

Continuous data presented as median and inter-quartile range.

TIMI risk score = age > 65 years, hypotension, tachycardia, Killip class II–IV, diabetes/hypertension/angina, anterior ST-elevation/LBBB, < 67 kg, time to treatment > 4 h. ACE, angiotensin-converting enzyme; ARB, angiotensin 1 receptor blocker; BMI, body mass index; I.c., intracoronary; PCI, primary percutaneous coronary intervention; Gp, glycoprotein; I.c., Intracoronar; TIMI, thrombolysis in myocardial infarction.

Table 2 CMR results

Characteristic	Total study cohort, <i>n</i> = 572	QRS distortion present (G3I+), <i>n</i> = 186	QRS distortion absent (G3I-), <i>n</i> = 386	P-value
Area at risk (%LV)	34.6 (25.4–47.3)	34.8 (26.1–48.1)	34.4 (25.3–47.0)	0.59
Infarct size (%LV)	17.3 (8.5–25.0)	18.3 (10.4–27.6)	16.5 (8.2–23.5)	0.01
Myocardial salvage index	50.9 (32.5–67.3)	47 (28–64)	53 (35–68)	0.01
Late MVO present, <i>n</i> (%)	282/558 (51)	99/180 (55)	183/378 (48)	0.15
Late MVO (%LV)	0.02 (0.0–0.09)	0.4 (0–2.7)	0 (0–1.5)	0.05
Hypointense core present (Haemorrhage)	175/503 (35%)	69/169 (41%)	106/334 (32%)	0.04
LV ejection fraction (%)	50.6 (43.6–57.7)	50.3 (43.5–57.3)	50.6 (43.9–57.9)	0.83

Continuous data presented as median and inter-quartile range.

CMR, cardiac magnetic resonance; LV, left ventricular; MVO, microvascular obstruction.

Likewise the patients with incomplete ST-R (<50%) were at higher risk for the occurrence of MACE (HR 2.1, 95% CI 1.09–4.08, $P = 0.03$).

In the multivariate Cox regression model, the presence of G3I emerged as an independent predictor of MACE. This was also true after inclusion of STR in the model (Table 5).

The inclusion of G3I in addition to the TIMI risk score resulted in an increase of the c-statistics from 0.69 to 0.73. However, this increase was not statistically significant ($P = 0.10$) (Figure 4). The inclusion of CMR markers of myocardial damage resulted in a significant increase of the c-statistic.

Discussion

To the best of our knowledge, this is the largest study to date investigating the association of G3I on pre-hospital ECG in STEMI patients with markers of myocardial damage assessed by CMR. The main findings of our study are as follows: (i) G3I is significantly associated with IS, myocardial salvage, MVO, and IMH after PCI, and (ii) G3I is a strong indicator of future cardiovascular events in a large multicentre high-risk STEMI population. Therefore, our data support the theory of an association of G3I with more severe myocardial and microvascular damage with subsequent adverse clinical outcome in acutely reperfused STEMI patients.

The ECG has been an essential part of the diagnosis, initial evaluation, and triage of patients with chest pain. The extent of STE and its resolution have been well investigated and are associated with IS and adverse outcomes.^{1,2} Recently we showed that the easy and quickly obtainable measure of the magnitude of STE in the worst residual lead after PCI is associated with CMR-defined myocardial damage and adverse outcome.³ Another easily assessable and potentially prognostic relevant ECG marker is the presence of the distortion of the terminal QRS complex (G3I).²⁰

G3I has been reported to be present between 19 and 53% of STEMI patients and has been associated with adverse clinical outcomes after thrombolysis and PCI.^{4,9,21,22} Mechanistically, G3I has been related to larger IS (biomarker and SPECT analysis),^{4,23} less myocardial salvage,²⁴ lower epicardial reperfusion success,²² and a greater extent of coronary artery disease.¹¹ However, most of these studies do not reflect contemporary infarction treatment, had small sample sizes, were single-centre investigations, and were performed mainly during the thrombolysis era. Therefore, further mechanistic and pathophysiological insights are needed to understand the prognostic significance of G3I. CMR is the ideal method to comprehensively evaluate the correlation of G3I with infarct characteristics and reperfusion injury. Two previous small single-centre studies ($n = 37$ and $n = 50$) investigated the relation of G3I with CMR-derived infarct characteristics.^{25,26} In line with these data, our study demonstrated that G3I is significantly associated with

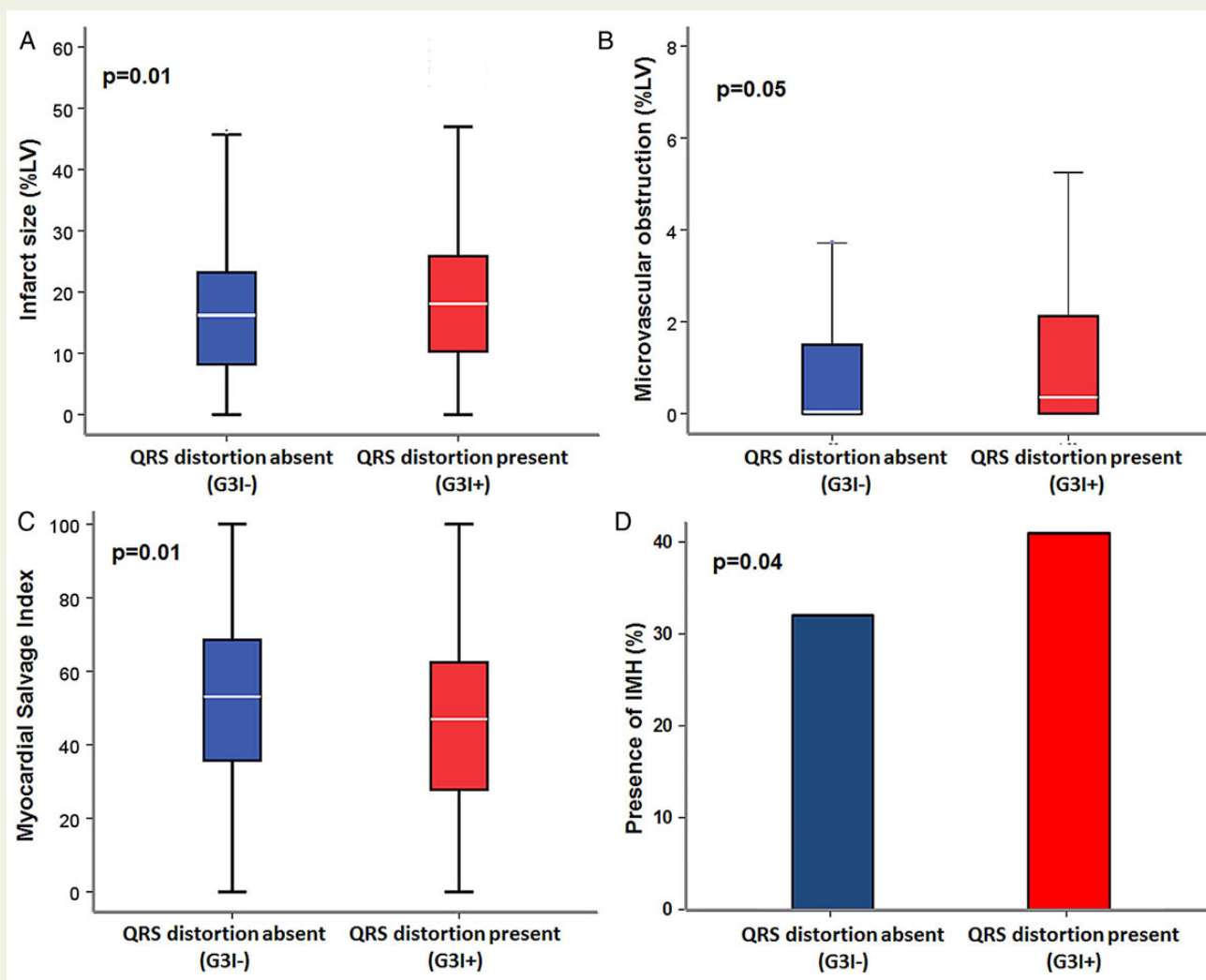


Figure 2 CMR results. Box (25th centile, median, and 75th centile) and whisker (10th and 90th centiles) plots of CMR outcomes according to the presence of QRS distortion (G3I) groups. (A) Infarct size. (B) Late microvascular obstruction. (C) Myocardial salvage index. (D) Presence of IMH.

Table 3 Predictors of QRS distortion (G3I) in univariable and stepwise multivariable logistic regression analysis

Variable	Univariable		Stepwise multivariable	
	Odds ratio (CI)	P-value	Odds ratio (CI)	P-value
Inferior infarction	1.71 (1.19–2.45)	0.003	2.18 (1.45–3.28)	0.002
Symptom onset to reperfusion	0.99 (0.98–1.00)	0.05	–	–
TIMI flow grade before PCI	0.78 (0.66–0.92)	0.003	–	–
Infarct size (%LV)	1.02 (1.01–1.03)	0.02	1.03 (1.01–1.04)	0.003
Microvascular obstruction (%LV)	1.06 (1.00–1.12)	0.06	–	–
Myocardial salvage index	0.98 (0.97–0.99)	0.02	–	–
Haemorrhage present	1.48 (1.01–2.18)	0.04	–	–

The table displays only significant variables in univariable logistic regression. All significant variables in univariate analysis were subsequently tested in a multivariable stepwise model. We excluded myocardial salvage index from multivariable analysis to avoid collinearity as myocardial salvage index has infarct size accounted for by its inclusion in the formula for its calculation.

CI, 95% confidence interval; LV, left ventricle; TIMI, thrombolysis in myocardial infarction.

Table 4 Clinical outcomes

	Total study cohort, n = 572	QRS distortion present (G3I+), n = 186	QRS distortion absent (G3I-), n = 386	P-value
MACE	45/572 (7.9%)	23/186 (12.3%)	22/386 (5.7%)	0.01
Death	14/567 (2.5%)	6/183 (3.3%)	8/384 (2.1%)	0.39
Re-infarction	17/567 (3.0%)	10/183 (5.5%)	7/384 (1.8%)	0.02
New heart failure	14/567 (2.5%)	7/183 (3.8%)	7/384 (1.8%)	0.15

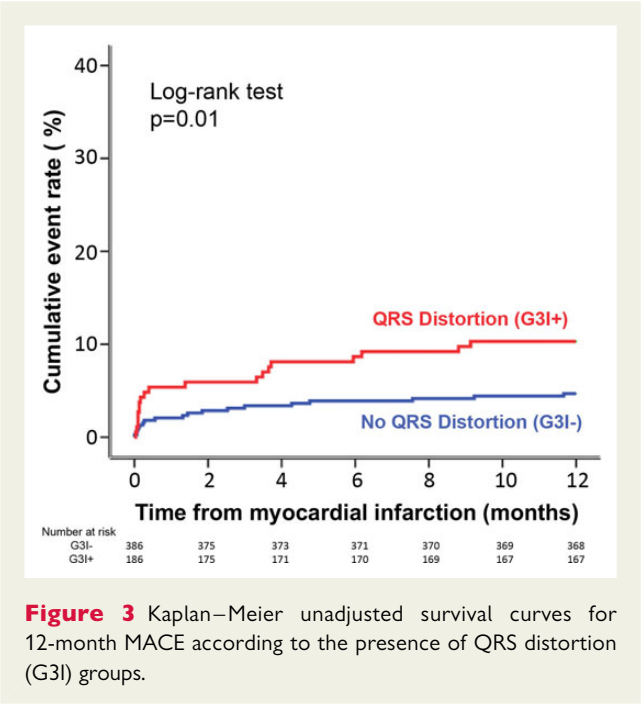


Figure 3 Kaplan–Meier unadjusted survival curves for 12-month MACE according to the presence of QRS distortion (G3I) groups.

IS, as well as MVO, LV function, and myocardial salvage. Our results therefore confirm the hypothesis that distortion of the terminal QRS complex is strongly associated with severe myocardial and microvascular injury in patients with STEMI. Consequently, more severe ischaemia and damage seem to occur when changes in the QRS configuration (as reflected by G3I) are detected in the ECG.

Although the AAR was comparable between groups and we observed a shorter ischaemic time in the G3I group, the presence of G3I was associated with larger infarcts, more MVO, and IMH. Moreover, an inferior infarct location was more frequent in patients with G3I and was even an independent predictor for the presence of G3I. Explanations for these findings are as follows: (i) Similar to Weaver *et al.*,²⁵ we found an association of G3I with impaired TIMI-flow pre-PCI, an important established predictor of survival in previous studies.²⁷ G3I seems to indicate complete occlusion of the infarct-related artery as reflected by low TIMI-flow grades with subsequent severe myocardial damage and risk for future cardiovascular events. (ii) It has been speculated that the presence of G3I is associated with a faster progression of irreversible tissue injury, caused by the absence of an intact collateral flow or ischaemic

preconditioning.^{21,22} Unfortunately, information on these variables were not systematically assessed in our study. (iii) Although many studies have linked anterior infarct location to G3I, a significant number of reports including our study have found the contrary.^{4,5,10} Inferior infarct location is generally accepted to be linked to a better prognosis, mostly because of smaller myocardium at risk and ISs in comparison to anterior MIs.^{28,29} The fact that G3I was linked to inferior infarcts and shorter ischaemic times emphasizes that this ECG pattern indicates extensive myocardial and microvascular damage, underlining its predictive value in the acute phase of STEMI even in early presenters and inferior infarctions.

The ability of G3I to early identify irreversible tissue damage and clinically relevant reperfusion injury is further supported by our clinical outcome findings. Patients presenting with a G3I pattern differed significantly in the occurrence of MACE, and G3I was an independent predictor of prognosis. Consequently, G3I was able to identify a high-risk subset of patients with worse 12-month clinical outcomes. The difference in occurrence of MACE between groups was mainly driven by a significant difference in the occurrence of re-infarctions and numerically lower rates of new CHF and death.

A higher risk of re-infarction with the presence of G3I has been well described.^{5,30} Recently Bakirci *et al.*²⁸ showed that patients with G3I have more complex coronary artery diseases as assessed by the Syntax Score, which might in part explain this phenomenon. Similarly, the development of MVO after MI is associated with the presence of thin-cap fibroatheromas²⁹ and limited collateral flow,³¹ indicating a more vulnerable coronary artery status which leads to a higher risk of recurrent ischaemia, as observed in patients with G3I.

Larger infarcts predispose to the development of heart failure and arrhythmogenic events. Although new CHF occurred numerically more often in the G3I group, this difference was not significant. This may be mainly attributed to our relatively small sample size and limited event rates. In the same way, we did not find a significant difference in mortality. Overall, mortality was significantly lower in our patients (2.5%) than described in previous studies investigating the clinical role of G3I, limiting statistical power. The more extensive use of treatment with stents (98%), thienopyridines (100%), and use of glycoprotein IIb/IIIa-inhibitors in almost all patients in our study might contribute to explain this observation.

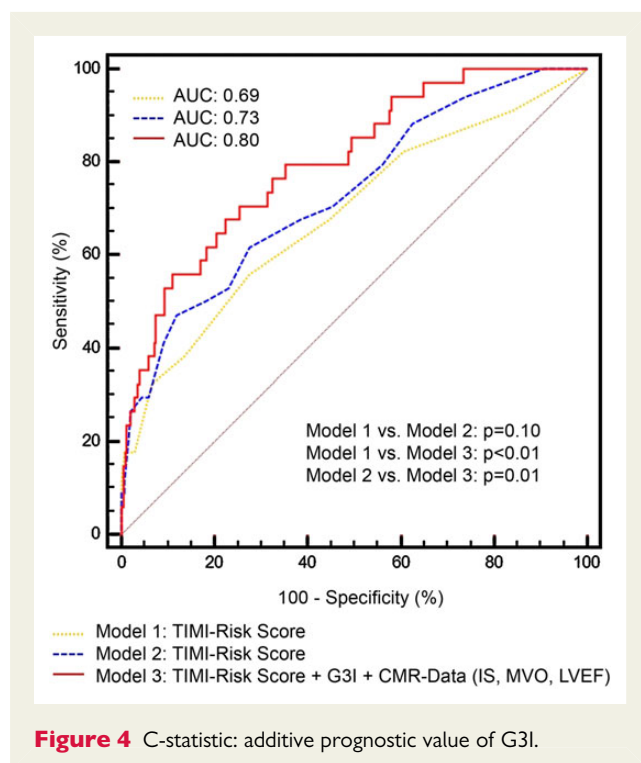
CMR markers of myocardial damage offered an additive prognostic value over and above G3I. The ECG parameter provides the advantage of being easily and widely available already at the initial diagnosis of STEMI.

Table 5 Predictors of MACE in univariable and stepwise multivariable Cox regression analysis

Variable	Univariable		Stepwise multivariable	
	Hazard ratio (CI)	P-value	Hazard ratio (CI)	P-value
Age	1.05 (1.02–1.08)	<0.001	1.05 (1.02–1.08)	0.004
Smoker	2.20 (1.01–4.77)	0.05	–	–
Number of diseased vessel	1.50 (1.07–1.97)	0.02	–	–
Killip-class on admission	1.92 (1.37–2.68)	<0.001	1.71 (1.18–2.48)	0.005
TIMI flow before PCI	0.72 (0.51–1.01)	0.003	–	–
ST-segment resolution (%)	0.99 (0.99–1.00)	0.02	–	–
QRS distortion present (G3I+)	2.27 (1.19–4.32)	0.01	2.19 (1.10–4.38)	0.03
LV ejection fraction (%)	0.92 (0.89–0.95)	<0.001	–	–
Infarct size (%LV)	1.04 (1.02–1.06)	0.001	1.03 (1.01–1.06)	0.02

The table displays only significant variables in univariable Cox regression. Myocardial salvage and MVO were not included in the model as myocardial salvage has infarct size accounted for by its inclusion in the formula for the calculation of myocardial salvage, and MVO strongly correlates with IS. All significant variables in univariate analysis were subsequently tested in a multivariable stepwise model.

CI, 95% confidence interval; LV, left ventricle; TIMI, thrombolysis in myocardial infarction.

**Figure 4** C-statistic: additive prognostic value of G3I.

Whether patients can further benefit from an implementation of the assessment of G3I to guide their management, for instance by a higher triage priority, the use of adjunctive therapies or a more intensive secondary prophylaxes needs to be further investigated.

Taken together our findings suggest that G3I is an important feature in the electrocardiographic evaluation of acute myocardial ischaemia, particularly given the correlation of this parameter with myocardial damage and prognosis in the current study.

However, further well-designed prospective studies are warranted to investigate the clinical utility of G3I.

Study limitations

Our results are based on relatively small patient numbers, despite being the largest CMR study to date assessing the relation of G3I with myocardial damage. Furthermore, the included patients were recruited from a randomized trial. Generalization might be precluded by specific inclusion criteria and treatment of exclusively Caucasian patients in specialized high-volume centres. Finally, IS and especially MVO are time dependent after acute STEMI. Thus, CMR timing is an important determinant for the presence and extent of MVO as well as IS. As the G3I groups underwent imaging after a similar time delay in our study, a potential bias is limited. A systematic assessment of death causes and arrhythmogenic events could have provided further insights in the connection between G3I and clinical outcomes.

In conclusion, G3I is significantly associated with IS, myocardial salvage, MVO, IMH, as well as MACE in a high-risk STEMI population. Therefore, this rapidly and easily assessable ECG parameter can accurately identify a high-risk patient population early in the course of STEMI, which could help to guide clinical management. The correlation of G3I with clinical prognosis is explained by its strong relation with severe myocardial and microvascular injury.

Authors' contributions

I.E. conceived the study and is guarantor. I.E., K.P.R., and H.B. analysed the data. M.G. performed CMR imaging. I.E. performed CMR analysis. All authors discussed, drafted, and revised the manuscript. The paper is exclusively submitted to *European Heart Journal—Cardiovascular Imaging* and is neither in consideration elsewhere nor has it been published previously. All authors have read and approved the manuscript.

Conflict of interest: None declared.

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