Relationship of Admission QRS Duration and Changes in QRS Duration With Myocardial Reperfusion in Patients With Acute ST Segment Elevation Myocardial Infarction (STEMI) Treated With Fibrinolytic Therapy

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Background Although ischemia induced QRS complex changes have been described previously, their relationship with impaired reperfusion, which is known to be associated with poor clinical outcomes, is not clear.

Methods and Results To investigate the relationship of QRS duration changes with myocardial reperfusion, we studied 165 acute myocardial infarction (MI) patients who were administered fibrinolytic therapy for reperfusion. For each patient, 12-lead electrocardiogram (ECG) with a paper speed of 50 mm/s was recorded on admission and repeated at the 60th and 90th min following fibrinolytic therapy. Based on the myocardial blush grades obtained from a control coronary angiography, patients were divided into reperfusion (grades 2, 3) and impaired reperfusion (grades 0, 1) groups. We detected impaired reperfusion in 74 patients. The patients in the impaired reperfusion group were older, more often diabetic, and had longer pain-to-needle intervals. They also had significantly longer QRS durations at admission compared to reperfusion group patients (91 ± 11 vs 79 ± 11 ms, $p < 0.001$). Reperfusion group patients showed significantly greater resolution in QRS duration at the 90th min post fibrinolysis ECG (18 ± 5 vs 5 ± 4 ms, $p < 0.001$). In regression analysis, the pain-to-needle time (odds ratio (OR): 0.55, 95% confidence interval (CI) 0.35–0.88, $p = 0.012$), QRS duration on admission (OR: 0.80, 95% CI 0.67–0.97, $p = 0.021$), and change in QRS duration at the post fibrinolysis 90th min ECG (OR: 2.43, 95% CI, 1.29–4.60, $p = 0.006$) were determined as independent predictors of adequate reperfusion.

Conclusion The present study, for the first time, has shown that admission QRS duration and post fibrinolysis 90th min QRS duration changes are related to tissue reperfusion in fibrinolytic administered acute MI patients. (Circ J 2008; 72: 873–879)

Key Words: Fibrinolytic therapy; QRS duration; Reperfusion

The primary goal of reperfusion therapy in acute ST segment elevation myocardial infarction (STEMI) is to achieve complete and sustained myocardial reperfusion in a timely fashion.¹ Nevertheless, after standard current fibrinolytic regimens, many patients have suboptimal reperfusion even after successfully restored infarct related artery (IRA) patency, possibly due to loss of microvascular integrity.^{2,3} While there is no definitely established advantage in routine immediate coronary angiography after thrombolytic administration,⁴ rescue therapy might benefit a limited proportion of patients with suboptimal reperfusion, if they

can be identified sufficiently early.⁵ Impaired reperfusion after acute myocardial infarction (MI), better known as no-reflow phenomenon, is associated with greater infarct size, an increased risk of death and left ventricular dysfunction.³ So, differentiation of a subgroup of acute MI patients who did not get benefit from fibrinolytic therapy by means of a practical, easily available and non-invasive diagnostic tool might have practical implications because this group of patients is likely to experience poorer outcomes.

Although the post fibrinolysis electrocardiogram (ECG) has shown promise as a non-invasive reperfusion marker, electrocardiographic assessment of reperfusion is traditionally based solely on changes of the ST segment. In contrast, a poor prognostic value of QRS prolongation in acute STEMI settings has been shown in previous studies.^{6,7}

Although in acute STEMI patients, ST segment elevation resolution for assessment of reperfusion status is in widespread use, to the best of our knowledge in fibrinolytic therapy administered patients, there are no reports evaluating the relationship of QRS duration with myocardial reperfusion. Thus, our objective in this study was primarily to investigate the relationship of admission QRS duration with myocardial reperfusion in fibrinolytic therapy administered

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acute STEMI patients. Second, we aimed to evaluate whether adequate reperfusion is associated with any change in QRS duration at 60th and 90th min post fibrinolysis ECGs. As the surrogate of tissue level reperfusion, we used angiographic myocardial blush grade, which was shown to be a reliable index of microvascular integrity in previous reports⁸⁻¹¹

Methods

From May 2005 to March 2007, 179 patients (mean age 59±10 years, 79% male) admitted with STEMI within 12 h from the onset of symptoms to Ankara Yuksek Ihtisas Hospital Cardiology clinic and Ankara Numune Hospital Cardiology clinic and who were administered front loaded tissue plasminogen activator (tPA) as reperfusion therapy, were primarily enrolled in the study. STEMI was defined as typical chest pain lasting more than 30 min along with ST segment elevation >1 mm in at least 2 consecutive electrocardiographic leads. We excluded patients older than 75 years, those with a recent history of stroke (within 3 months), those with active bleeding or bleeding diathesis, those with a recent history of trauma or major surgery (within a month), those with suspected aortic dissection, those receiving oral anticoagulant therapy with coumarin derivatives, and those with severe, uncontrolled hypertension (defined as a systolic blood pressure of more than 180 mmHg that was unresponsive to therapy). Patients who were in shock, treated with fibrinolytic therapy in the previous 24 h, patients with a history of coronary artery bypass grafting and patients with bundle branch blocks and patients who had severe ST segment elevation obscuring J point identification were also excluded from the study. The study was approved by each center's institutional local ethics committee and all patients gave their written informed consent.

Intravenous fibrinolytic therapy was administered as a bolus dose of 15 mg of tPA (Actilyse, Boehringer Ingelheim, Ingelheim, Germany) followed by a 90-min infusion in which 0.75 mg/kg of body weight was given over a period of 30 min, followed by 0.5 mg/kg over a period of 60 min. They also received intravenous heparin for a period of 48–72 h; the initial dose was 1,000 U/h, and the dose was adjusted to obtain an activated partial-thromboplastin time between 60 and 85 s. All patients received 300 mg of oral aspirin and 5,000 U of IV heparin on admission. Other medications were administered according to the discretion of the treating physicians.

Electrocardiographic Evaluation

For each patient, 12 lead ECG with a paper speed of 50 mm/s and amplification of 10 mm/mV was recorded by using a delta 60 plus E (Remco Italia, Italy) ECG machine on admission and it was repeated at the 60th and 90th min following fibrinolytic therapy. ECGs were coded and all annotations were masked. QRS duration, from the onset to the J point, was measured manually with the help of a caliper and magnifying lens in 3 consecutive beats in the infarct-related leads by 2 of the investigators unaware of the reperfusion status of the patient. For each of the infarct-related leads, means of 3 beats were calculated and the mean value for QRS duration in infarct-related leads was computed. The average values of QRS duration measurements obtained by the 2 investigators were used for statistical analysis. Interobserver coefficients of variation for admis-

sion and postfibrinolysis at the 60th and 90th min ECG QRS durations were found to be 4.4, 4.8 and 5.3%, respectively. Change in QRS duration was calculated by subtracting the post fibrinolysis QRS duration from the admission QRS duration. The summed ST segment elevation was measured by summing the ST amplitude in all leads with the ST elevation at baseline using methods described previously.¹²

Angiographic Analysis

Cardiac catheterization was performed at a mean of 3 days after the myocardial infarct. Selective left and right coronary angiography and left ventriculography were performed in all eligible patients. Thrombolysis In Myocardial Infarction (TIMI) flow grades were assessed as previously described.¹³ TIMI myocardial perfusion (TMP) grade was determined on angiogram by 2 blinded experienced interventional cardiologists based on the visual assessment of contrast opacification of the myocardial territory subtended by the IRA or the vessel supplying collateral channels to the IRA, in the cases when occluded IRA was present, as previously described.¹⁰ If discordance regarding TMP grade was present, a third reader's opinion was sort. TMP grade was defined as follows: (0) no myocardial blush or contrast density; (1) minimal myocardial blush or contrast density; (2) moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-IRA; and (3) normal myocardial blush comparable with that obtained during angiography of a contralateral or ipsilateral non-IRA. TMP grades 0 and 1 were taken as indicators of injured microvasculature and TMP grades 2 and 3 were taken as indicators of preserved microvasculature, as previously described.¹⁰

Statistical Analysis

Continuous data were presented as mean±SD. Differences in continuous variables between the groups were determined by the Student's t-test or the Mann–Whitney U-test for variables with or without normal distribution, respectively. To test normal distribution of continuous variables, the 1 sample Kolmogorov–Smirnov test was utilised. Categorical variables were presented as percentages and compared using the chi-square test or Fisher's exact test. The Spearman correlation coefficient was calculated to evaluate the association between 2 continuous variables. For factors found to be related to impaired reperfusion in univariate analysis, regression analyses using a backward elimination technique were performed to determine their impact independently. The odd's ratios (OR) were calculated with 95% confidence intervals (CI). For determining the predictive impact of admission QRS duration on development of impaired reperfusion, receiver operating characteristics (ROC) analyses was performed. The best cut-off value was determined and at that point, sensitivity and specificity was determined. A probability value of $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS 11.5 (SPSS Inc, Chicago, IL, USA).

Results

Of the patients enrolled, 2 died without undergoing angiography, an additional 7 patients did not undergo cardiac catheterization for other reasons (refusal by the patient, a decision by the physician, or a clinical contraindication), and the data were incomplete for 5 patients. Therefore, the results of a total of 165 patients were taken into account for

Table 1 Comparison of Reperfusion and Impaired Reperfusion Group Patients According to Baseline Demographic and Angiographic Parameters

	Reperfusion group (n=91)	Impaired reperfusion group (n=74)	p value
Age (years)	58±10	61±9	0.045
Male gender (%)	72 (79)	58 (78)	0.908
Systemic hypertension (%)	30 (33)	28 (38)	0.515
Diabetes mellitus (%)	15 (17)	22 (30)	0.042
Active smokers (%)	37 (41)	23 (31)	0.203
Pain-to-needle time (h)	3.3±2.1	6.2±2.8	<0.001
Heart rate (beats/min)	74±14	79±15	0.062
Systolic BP (mmHg)	128±23	130±31	0.582
Killip class on presentation (%)			
I	85 (93)	62 (84)	0.143
II-III	6 (7)	12 (16)	
MI subgroup (%)			
Anterior wall	47 (52)	50 (68)	0.039
Non-anterior wall	44 (48)	24 (32)	
Prior MI history (%)	10 (11)	10 (13)	0.768
TIMI flow in IRA (%)			
TIMI 0/1	3 (3)	39 (53)	<0.001
TIMI 2	4 (5)	10 (13)	
TIMI 3	84 (92)	25 (34)	
Multivessel disease (%)			
1 vessel	41 (45)	37 (50)	0.686
2-3 vessel	50 (55)	37 (50)	
Peak CK-MB (IU/L)	257±120	293±114	0.050

BP, blood pressure; MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; IRA, infarct related artery; CK-MB, creatinine kinase MB fraction.

Table 2 Comparison of Reperfusion and Impaired Reperfusion Groups According to Electrocardiographic Parameters

	Reperfusion group (n=91)	Impaired reperfusion group (n=74)	p value
Sum of ST elevations on admission (mm)	12±7	11±6	0.354
Sum of ST depressions on admission (mm)	3±3	4±2	0.060
QRS duration on admission (ms)	79±11	91±11	<0.001
QRS duration at the post fibrinolysis 60 th min ECG (ms)	71±11	89±12	<0.001
QRS duration at the post fibrinolysis 90 th min ECG (ms)	61±11	86±12	<0.001
QRS narrowing at the post fibrinolysis 60 th min ECG (ms)	8±4	2±2	<0.001
QRS narrowing at the post fibrinolysis 90 th min ECG (ms)	18±5	5±4	<0.001

ECG, electrocardiogram.

statistical analysis. Grade 2/3 TMP was detected in 91 (55%) patients (16 patients with grade 2 and 75 patients with grade 3) and these patients constituted the reperfusion group and those 74 patients having grade 1/2 TMP (33 patients with grade 1 and 41 patients with grade 0) formed the impaired reperfusion group. A comparison of patients' baseline clinical and angiographic characteristics between reperfusion and impaired reperfusion groups are presented in Table 1.

While the 2 groups were similar in terms of gender, smoking habits and history of hypertension, we detected significant differences in terms of age, presence of diabetes mellitus (DM) and pain-to-needle time. The patients in the impaired reperfusion groups were older (61±9 vs 58±10 years, $p=0.045$), were more likely to be diabetic (30% vs 17%, $p=0.042$) and had longer pain-to-needle interval (6.2±2.8 vs 3.3±2.1 h, $p<0.001$) when compared to patients in the reperfusion group. Also, the patients in the impaired reperfusion group were more likely to have anterior MI (68% vs 52%, $p=0.039$). Heart rate, blood pressure and the Killip class of patients on admission did not differ between the groups.

When angiographic parameters were taken into account, there was a significant difference between the groups regard-

Fig 1. Distribution of admission QRS duration of patients in the impaired reperfusion and reperfusion groups.

Fig2. Distribution of the amount of change in QRS duration according to postfibrinolysis 90th min electrocardiogram (ECG) between the groups.

Fig3. Distribution of QRS narrowing at the 90th min electrocardiogram (ECG) among subgroups according to thrombolysis in myocardial infarction (TIMI) grades.

Table 3 Independent Predictors of Reperfusion in Regression Analysis

		OR (95%CI)	p value
Pain-to-needle time (h)	-0.594	0.55 (0.35–0.88)	0.012
QRS duration on admission (ms)	-0.219	0.80 (0.67–0.97)	0.021
QRS narrowing at the post fibrinolysis 90 th min ECG (ms)	0.889	2.43 (1.29–4.60)	0.006

OR, odds ratio; CI, confidence interval. Other abbreviation see in Table 2.

ing TIMI flow grade in IRA. As presented in Table 1, the TIMI flow grade 3 (complete epicardial flow) in IRA was present in 92% of patients with adequate reperfusion and in 34% of patients with impaired reperfusion ($p<0.001$).

ECG Findings

When we compared the groups in terms of electrocardiographic parameters (Table 2), although we could not detect any difference between the groups regarding total sum of ST elevations and sum of ST depressions on admission, as presented in Fig 1, there was a significant difference when QRS duration on admission was considered. Patients in the impaired reperfusion group had significantly longer QRS durations at admission compared to reperfusion group patients (91 ± 11 vs 79 ± 11 ms, $p<0.001$). On correlation analysis, the admission QRS duration was found to correlate positively with age ($r=0.180$, $p=0.021$) and pain-to-needle interval ($r=0.500$, $p<0.001$). When we analysed QRS durations on post fibrinolysis ECGs from the 2 groups, QRS duration was found to be longer in the impaired reperfusion group compared to the reperfusion group, at both post fibrinolysis 60th (89 ± 12 vs 71 ± 11 ms, $p<0.001$) and 90th min ECGs (86 ± 12 vs 61 ± 11 ms, $p<0.001$).

When we took into account the amount of change in QRS duration, that is, admission QRS duration minus post fibrinolysis QRS duration, we detected a significant difference between reperfusion and impaired reperfusion groups at both post fibrinolysis 60th (8 ± 4 vs 2 ± 2 ms, $p<0.001$) and 90th min ECGs (18 ± 5 vs 5 ± 4 ms, $p<0.001$). The mean change in QRS duration was more prominent at the 90th min ECG compared to the 60th min post-fibrinolysis ECG (12 ± 8 vs

5 ± 5 ms, $p<0.001$). Fig2 illustrates the comparison of the amount of change in QRS duration according to the 90th min post fibrinolysis ECG between the groups.

On correlation analysis, admission QRS duration ($r=-0.368$, $p=0.001$) and pain-to-needle time ($r=-0.444$, $p=0.001$) were found to be significantly, negatively correlated with QRS narrowing at the post fibrinolysis 90th min ECG. More importantly, we detected a strong positive correlation between QRS narrowing at the post fibrinolysis 90th min ECG and TIMI grade ($r=0.873$, $p<0.001$). In Fig 3, the box plot graphic illustrating the distribution of QRS narrowing at the 90th min ECG among subgroups according to TIMI grades is shown.

To understand the independent impact of individual variables that were found to be related to reperfusion in univariate analysis, we performed regression analysis including age, pain-to-needle interval, DM, anterior MI localization, QRS duration on admission, change in QRS duration at the post fibrinolysis 60th and 90th min ECGs and TIMI flow grade in IRA variables. After adjustment for TIMI flow grade, pain-to-needle time (OR: 0.55 95% CI 0.35–0.88, $p=0.012$), QRS duration on admission (OR: 0.80, 95% CI 0.67–0.97, $p=0.021$) and change in QRS duration according to the post fibrinolysis 90th min ECG (OR: 2.43, 95% CI, 1.29–4.60, $p=0.006$) were found as independent predictors of adequate myocardial reperfusion in our study group (Table 3). While pain-to-needle time and QRS duration on admission were independent negative factors, the change in QRS duration according to the post fibrinolysis 90th min ECG was a positive factor for adequate reperfusion, as presented in Table 3.

To determine the best cut-off value for the admission

QRS duration for predicting impaired reperfusion ROC analyses was performed; area under the ROC curve with admission QRS duration used to detect impaired reperfusion was 0.78 (95% CI 0.70–0.85, $p < 0.001$). From that analysis, a QRS duration value of 83 ms was determined to be best discriminating value for impaired reperfusion. An admission QRS duration value of 83 ms had a sensitivity of 77% and specificity of 71% in predicting impaired reperfusion after thrombolytic treatment.

Discussion

Summary of Findings

Among the clinical variables analysed in this report, age, pain-to-needle time, having DM, anterior MI localization, and among the ECG parameters, QRS duration on admission and QRS narrowing at the post fibrinolysis 60th and 90th min ECGs were found to be related to adequate reperfusion in univariate analysis. In multivariate analysis, pain-to-needle time, QRS duration on admission and amount of QRS narrowing at the post fibrinolysis 90th min ECG were detected as independent predictors of adequate reperfusion.

To the best of our knowledge, this study represents the first investigation in the literature showing the association of admission QRS duration with the development of reperfusion abnormalities at tissue level following fibrinolytic therapy. Furthermore, the association of the post fibrinolysis 90th min QRS narrowing on ECG with adequate reperfusion was shown for the first time in the literature.

In this report, which is in accordance with current related literature, we have verified that a substantial number of the patients (45%) had impaired tissue level reperfusion (TMP grade 0/1) after fibrinolytic therapy, despite an achievement of IRA patency (TIMI 2,3 flow) in 74% of study group patients, implying that achievement of epicardial patency does not guarantee normal myocardial reperfusion. The exact cause of reperfusion abnormalities faced after acute MI is not clearly known, but it has been largely attributed to microvascular dysfunction¹⁴ which initiates with the onset of ischemia and extends up to 48 h afterward. Previously, impaired myocardial reperfusion has been shown to be a major predictor of adverse outcomes in patients undergoing reperfusion therapy³ and in the literature; several modalities including myocardial contrast echocardiography,¹⁵ positron emission tomography,¹⁶ the angiographic myocardial blush grade,⁸ doppler flow wire measurements¹⁷ and the resolution of ST-segment elevation on the 12-lead ECG¹⁸ have been suggested to assess myocardial reperfusion.

In this study, as a surrogate of reperfusion, we used a myocardial blush as the TMP grade, which was previously shown to be related to enzymatic infarct size, the extent of ST segment elevation resolution, left ventricular function, long-term mortality⁸ and degree of myocardial salvage assessed by scintigraphy^{9,11} in patients with acute MI. We used TMP grades obtained from coronary angiograms that were performed at a mean of 3 days after acute MI. Considering the time-course of reperfusion injury, which initiates after the restoration of blood flow in the IRA and lasts up to 48 h after acute MI onset,¹⁴ it is possible to propose that the assessment of myocardial reperfusion at a later stage of acute MI (after day 1) might reflect the final steady state status more accurately.^{11,19}

Interpretation of ECG Findings

In the present study, QRS complex changes, which prob-

ably are overlooked by much more prominent ST-segment changes, in daily clinical practice were analyzed to determine if these changes that are rarely used clinically, relate to myocardial reperfusion after fibrinolytic treatment, in the setting of acute STEMI.

In agreement with our findings, QRS prolongation, which is associated with ischemia, was reported in experimental models as well as in human studies.^{20,21} In a recent study by Weston et al²⁰ conducted on dogs undergoing experimental coronary occlusion, QRS prolongation following coronary occlusion and its adverse implications on myocardial salvage had been reported. Similarly, Cantor et al²¹ reported QRS prolongation in majority of their study group patients undergoing percutaneous transluminal coronary angioplasty and they reported greater prolongation in QRS duration when proximal and middle segments of major arteries were occluded. Similarly transient QRS prolongation during typical anginal pain in patients having documented coronary artery disease was shown by Michaelides et al²² using signal-averaged ECG.

In contrast, a wider QRS duration might be a reflection of more extensive damage to the myocardium and a greater amount of infarction.²³ A moderate positive correlation was detected between admission QRS duration and pain-to-needle interval, which is in support of this association. Accordingly, in post MI patients, the association of QRS prolongation with adverse cardiovascular events has been reported.^{6,7,23}

During coronary occlusion, the most likely underlying physiologic mechanism of QRS prolongation is the slowing of conduction within areas of ischemia.²⁰ In experimental models of myocardial ischemia, demonstration of the association of QRS prolongation with Purkinje-ventricular conduction delay is further support for this mechanism.^{24–26} Consistently, the correlation we detected between admission QRS duration and ischemia duration in our study group is in favour of the idea of ischemia as a mechanism of QRS prolongation. QRS prolongation might be a sign of extensive ischemia and a poor metabolic state, which was shown to worsen with the delay in reperfusion.^{6,27} Late reperfusion was previously found to be associated with impaired reperfusion, larger infarct size and higher mortality, even after achievement of TIMI 3 flow.²⁷

In patients with STEMI, QRS prolongation was considered to be a mainly dynamic phenomenon induced by ischemia and likely to be relieved by successful reperfusion.⁶ Our finding of more significant narrowing in QRS duration in the reperfusion group is in support of this dynamic nature of change in QRS duration showing resolution after successful reperfusion. The correlation we observed between QRS narrowing and pain-to-needle time is another factor of support for this dynamic nature of QRS changes. We proposed that in patients with a longer ischemic period, irreversible microvascular damage had occurred and such patients had longer QRS durations at admission, and less or no change in QRS duration was observed in these patients reflecting impaired reperfusion. To attain adequate myocardial reperfusion, in addition to a patent IRA, anatomically and functionally preserved microvasculature is needed. Similar QRS duration changes in a primary angioplasty setting was reported by Tsukahara et al⁶ who noted normalization of QRS duration within 24 h of successful angioplasty in 79% of patients having intermediately prolonged QRS duration at admission. Reversal of ischemia induced electrocardiographic changes are regarded as a functional index of the

electrical activity of the jeopardized myocardium, and electrocardiographic indices of reperfusion was suggested to be a better representation of microvasculature status²⁸

Conclusion

Identification of acute STEMI patients who are expected to be at a higher risk of impaired reperfusion after fibrinolytic therapy by means of an easy, simple, bed-side applicable diagnostic modality might provide help in the discrimination of a higher risk patient subgroup and also identify those subjects who benefit most from rescue interventions. In this study, we have shown the association of admission QRS duration with impaired reperfusion. Based on our findings, acute STEMI patients having QRS duration values above 83 ms should be considered to be at a higher risk of impaired reperfusion after lytic therapy. Perhaps for these patients, as initial revascularisation modality, primary percutaneous interventions, which was shown to be a more direct, rapid and effective means of attaining IRA patency, should be considered. Taking into account our finding of a post fibrinolysis greater resolution in QRS duration in the adequate reperfusion group compared to the impaired reperfusion group, it is possible to suggest that these QRS duration changes are reflections of a dynamic nature of the ischemia and reperfusion process in acute MI settings. In acute STEMI settings, it should be investigated further whether algorithms, combining QRS duration changes with ST segment changes for assessment of the myocardial reperfusion, might be more helpful in early risk stratification and provide a better discrimination of patients who require rescue intervention.

Study Limitations

This was a small-sized study and there was not a clear standardised method for the measurement of QRS duration, which has normal range of 60–80 ms. In the presence of abnormalities of both waveforms, it is often difficult to precisely determine the junction between the end of the QRS complex and the beginning of the ST segment. Second, in this study, we used TMP grade as a surrogate of tissue reperfusion. Using another modality to define reperfusion could change the distribution of patients among the reperfusion or impaired reperfusion groups. In addition, this study included patients reperfused by fibrinolytic treatment. It must be investigated whether our findings can be extrapolated to an angioplasty group. One drawback of the current study comes from the manual measurement of QRS duration. The use of automated or computerized ECG measurement techniques might help in the standardisation of QRS duration measurements in future studies.

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