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)

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Previous studies have shown an association between distortion of the terminal portion of the QRS (QRS[+] pattern: emergence of the J point ≥50% of the R wave in leads with qR configuration, or disappearance of the S wave in leads with an Rs configuration) on admission and in-hospital mortality in acute myocardial infarction (AMI). However, the mechanism for this association is not known. We assessed the relation between QRS(+) pattern and coronary angiographic findings, infarct size, and long-term prognosis in the Thrombolysis In Myocardial Infarction 4 trial. Patients were allocated into 2 groups based on the presence (QRS[+], n = 85) or absence (QRS[−], n = 293) of QRS distortion. The QRS(+) patients were older (mean ± SD: 61.1 ± 10.6 vs 57.5 ± 10.6 years, p = 0.004), had more anterior AMI (49% vs 37%, p = 0.04), and less previous angina (42% vs 54%, p = 0.05). QRS(+) patients had larger infarct size as assessed by creatine kinase release over 24 hours (209 ± 147 vs 155 ± 129, p = 0.003), and predischarge sestamibi (MIBI) defect (17.9 ± 15.9% vs 11.2 ± 13.4%, p <0.001). When adjusting for difference in baseline characteristics, p values for the differences in 24-hour creatine kinase release were 0.03 and 0.64 for anterior and nonanterior AMI, respectively, and for MIBI defect size 0.03 and 0.02, respectively. One-year mortality (18% vs 6%, p = 0.03) was higher and the weighted end point of death, reinfarction, heart failure, or left ventricular ejection fraction <40% (0.33 ± 0.37 vs 0.24 ± 0.32, p = 0.13), tended to be higher in the anterior AMI patients with QRS(+). No difference in clinical outcome was found in patients with non–anterior AMI. These findings suggest that this simple electrocardiographic definition of presence of QRS(+) pattern on admission may provide an early estimation of infarct size and long-term prognosis, especially in anterior AMI.

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The decision whether to proceed with reperfusion therapy in a patient with suspected acute myocardial infarction (AMI) should be reached within minutes after admission. At the time this decision is made, the only tools generally available are the history, physical examination, and electrocardiogram. Previous studies on the association between the admission electrocardiogram of patients with AMI and either the ischemic area at risk, final infarct size, or prognosis have concentrated on the magnitude of ST-segment deviation or number of leads with ST-segment elevation.[1–5] The best correlation between infarct size and admission electrocardiogram was found using the number of leads with ST elevation in anterior wall AMI and the magnitude of ST elevation in inferior wall AMI.[4,5] This correlation, however, is only weak[5,6] and is more related to the collateral score.[5] In previous studies, little attention was paid to changes in the QRS morphology. Previously we reported that distortion of the terminal portion of the QRS on admission is associated with an increased in-hospital mortality.[7,8] The mechanism responsible for the association between terminal QRS distortion and adverse outcome and whether it is related to myocardial infarct size is unknown. We further investigated this phenomenon in a multicenter thrombolytic trial.

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METHODS

Study protocol: The Thrombolysis in Myocardial Infarction (TIMI) 4 trial[9] provided the opportunity to determine the relation between the distortion of the terminal portion of the QRS on admission in patients with AMI and (1) findings on the coronary angiogram, (2) estimation of infarct size, (3) left

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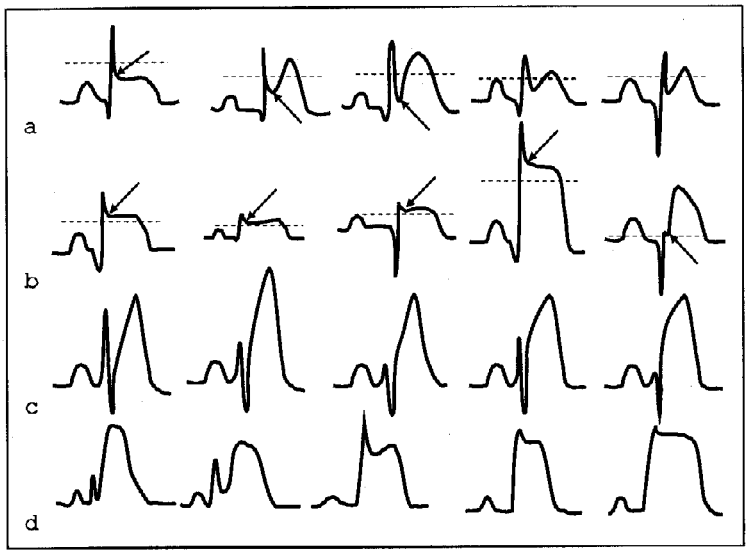

FIGURE 1. Illustrations of electrocardiographic complexes without *(lines a and c)* and with *(lines b and d)* terminal QRS distortion. Terminal QRS distortion (QRS[+]) is defined as emergence of the J point ≥50% of the R-wave amplitude in leads with qR configuration or disappearance of the S wave in leads with an Rs configuration. To be included in the QRS(+) group, at least 2 adjacent leads demonstrated terminal QRS distortion. Line a: QR complexes with QRS(−) pattern. Despite different degree of ST-segment elevation, in all complexes the J point *(arrow)* emerges below 50% of the R-wave amplitude *(dashed line)*. Line b: QR complexes with QRS(+) pattern. In all complexes, the J point emerges above 50% of the R-wave amplitude. Line c: RS complexes with QRS(−) configuration (leads V_1 to V_3). In all complexes the S wave is preserved (compared with line d). Line d: complexes in leads usualy demonstrating RS pattern (V_1 to V_3) with QRS(+) pattern showing different magnitude of ST-segment elevation. However, in all complexes S wave disappeared.

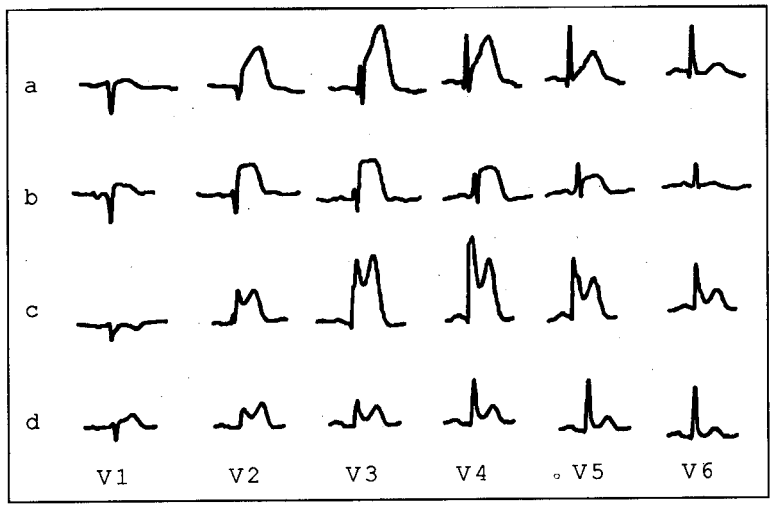

FIGURE 2. Admission electrocardiograms of 4 patients with anterior wall acute myocardial infarction (recorded at a paper speed of 25 mm/s; sensitivity: 1 mV = 10 mm). Examples *a* and *b* are of QRS(−) pattern. Despite having a high degree of ST-segment elevation, the S waves in leads V_2 and V_3 are preserved and the J points emerge below 50% of the R waves. Examples *c* and *d* are of QRS(+) pattern. Despite having a different magnitude of ST-segment elevation, in both examples the S waves in leads V_2 and V_3 disappeared, and in example *c* the J points in leads V_2 and V_3 emerge at >50% of the R-wave height.

ventricular function, and (4) short- and long-term prognosis. The TIMI 4 trial was a randomized, double-blind, multicenter study designed to assess outcome after front-loaded tissue plasminogen activator, anistreplase, and a combination of the 2 in patients with AMI. Inclusion criteria were: age <80 years, typical chest pain lasting >30 minutes within 6 hours before entry to the trial, and electrocardiographic changes of AMI (ST elevation of at least 0.1 mV in 2 adjacent leads or new left bundle branch block). Exclusion criteria were: contraindication to thrombolytic therapy, recent coronary bypass surgery, previous use of streptokinase or anistreplase, chronic left bundle branch block, women of childbearing potential, use of oral anticoagulation therapy, and presence of any other serious disease.

In this retrospective analysis of QRS morphology we included only patients with upright T waves in the leads with ST-segment elevation. Patients with flat or inverted T waves in the leads demonstrating ST-segment elevation were excluded, because this represents a more advanced electrocardiographic stage of AMI, and it has been reported that early T-wave inversion may signify reperfusion.[10] Patients with bundle branch block, intraventricular conduction defects, or ventricular rhythm were also excluded.

Patients were followed-up in the hospital for clinical events.[9] Serum creatine kinase levels were determined upon initiation of therapy and at 8, 16, and 24 hours thereafter. For calculation of creatine kinase release over the first 24 hours, creatine kinase values were expressed as multiples of the upper limit of normal at each participating hospital, and calculation of the area under the creatine kinase–time curve over the first 24 hours was performed as previously described.[11] Thus, the units are multiples of upper limit of normal hours. Coronary angiography was obtained at 90 minutes after initiation of thrombolytic therapy and repeated 18 to 36 hours thereafter. Coronary arteriograms were interpreted by quantitative analysis in the angiographic core laboratory. Predischarge radionuclide ventriculogram and myocardial perfusion scintigraphy using technetium-99m sestamibi (MIBI) scan were obtained according to a standardized protocol. Scans were interpreted at the Radionuclide Core Laboratory at Yale University. The integrated MIBI defect size was expressed as percent defect compared with normal perfusion scan.[12] Telephone follow-up, obtained at 6 weeks and 1 year, was complete in 96% of patients.[9]

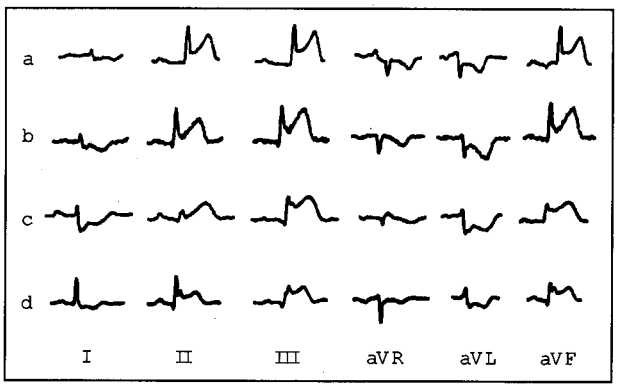

FIGURE 3. Admission electrocardiograms of 4 patients with inferior wall acute myocardial infarction (recorded at a paper speed of 25 mm/s; sensitivity: 1 mV = 10 mm). Examples *a* and *b* are of QRS(−) pattern. The J points in leads II, III, and aVF emerge at <50% of the R-wave height. Examples *c* and *d* are of QRS(+) pattern, because the J points in leads III and aVF emerge at >50% of the R-wave height.

Electrocardiographic evaluation: All admission electrocardiograms were analyzed by one of the authors (Y.B.), who had no knowledge of the clinical, angiographic, and scintigraphic data. Patients were allocated into the following 2 groups:

QRS-POSITIVE (+) GROUP: Patients had tall, symmetric, upright T waves and ST-segment elevation, accompanied by distortion of the terminal portion of the QRS complex in ≥2 adjacent leads: (1) in leads with initial QR configuration, emergence of the J point at ≥50% of the R-wave amplitude (as measured from the isoelectric line); or (2) in leads without Q waves (Rs configuration), absence of S waves (e.g., leads V_1 through V_3[7,8] (Figures 1 to 3).

QRS-NEGATIVE (−) GROUP: Patients had tall, symmetric, upright T waves and ST-segment elevation in ≥2 adjacent leads, without major changes in the morphology of the terminal portion of the QRS complex (Figures 1 to 3).

Study end points: The primary end points for our electrocardiographic analysis were estimation of infarct size by: (1) peak creatine kinase levels, (2) creatine kinase release over 24 hours (multiples of upper limit of normal-hours), (3) predischarge MIBI defect size (percentage of defect compared with normal perfusion scans), and (4) left ventricular ejection fraction (measured by radionuclide ventriculogram).

Secondary end points were in-hospital mortality, cumulative 1-year mortality, and the composite outcome of in-hospital death, recurrent AMI, severe congestive heart failure or cardiogenic shock, and ejection fraction <40%. In addition, a weighted composite end point was calculated for each patient using the event with the highest score: death (weight = 1.0), heart failure (weight = 0.8), left ventricular ejection fraction <40% (weight = 0.6), reinfarction (weight = 0.5), and none (weight = 0), as previously described.[13]

In addition, QRS(+) and QRS(−) groups were compared regarding the angiographic data: location of the infarct related artery; presence of 1-, 2-, or 3-vessel disease; 90-minute TIMI grade flow; residual stenosis; and presence of visible collateral circulation at 90 minutes.

Statistical analysis: Statistical analyses were carried out by the Data Coordinating Center at the Research Triangle Institute. Chi-square tests were used to determine the significance of the differences between proportions for discrete variables. The mean ± SD and median are presented for continuous variables. In the case of continuous variables, differences between the QRS(+) and QRS(−) groups were analyzed for statistical significance by Wilcoxon's rank-sum test. All tests of significance were 2-tailed. A p value <0.05 was considered statistically significant. Multivariate regression analyses of the infarct size data (creatine kinase release over 24 hours and MIBI defect size) were used to determine the importance of distortion of the QRS on admission (QRS[+] vs QRS[−] groups) for anterior and non–anterior wall AMI separately. The multivariate regression analysis was adjusted for a set of baseline variables, available on admission: treatment assignment, age, gender, previous AMI, previous angina, presence of pulmonary rales, third heart sound, and time from onset of pain to therapy.

RESULTS

Baseline characteristics of the patients: The TIMI 4 trial population, including an open-label pilot phase, encompassed 416 patients. We excluded 38 patients from this analysis because of the presence of intraventricular conduction defects, including bundle branch blocks (n = 21) and negative T waves in the leads with ST elevation (n = 15). Two patients did not have qualifying electrocardiograms available.

The study population included 378 patients: 85 patients with QRS(+) and 293 patients with QRS(−) pattern (Table I). QRS(+) patients were older, had a higher incidence of anterior wall AMI, and were treated earlier than the QRS(−) group. However, no differences in gender or prevalence of hypertension or diabetes mellitus were found between the groups. QRS(−) patients exhibited a trend toward more previous AMI and previous angina pectoris. The percentages of patients ever having smoked, as well as those currently smoking, were similar. No differences between the groups were found regarding medications given before the index admission, in the evidence of left ventricular failure at enrollment, or treatment assignment (not shown).

Estimation of infarct size: Peak serum creatine kinase was higher in the QRS(+) than the QRS(−) group (Table II). Creatine kinase release over 24 hours was significantly higher in the QRS(+) than the QRS(−) patients. Both differences were statistically significant only in the anterior wall AMI patients, although there were similar trends in the non–anterior AMI patients. After adjustment for all baseline variables listed in Table I in a multivariate regression analysis, QRS(+) pattern continued to be

TABLE I Baseline Characteristics of Patients Without Versus With Distortion of the Terminal Portion of the QRS

	QRS (+) Group n = 85	QRS (−) Group n = 293	
	No. (%)	No. (%)	p Value
Men	58 (68)	224 (76)	0.13
Age (yr)			
Mean ± SD	61.1 ± 10.6	57.5 ± 10.6	0.004
Median (range)	61 (30–78)	57 (28–79)	
Previous infarction	7 (8)	46 (16)	0.08
Previous angina	36 (42)	159 (54)	0.05
Ischemic pain <48 h	21 (84)*	79 (78)*	0.52
Prior coronary bypass	2 (2)	10 (3)	0.62
Hypertension (requiring treatment)	27 (32)	104 (36)	0.54
Diabetes mellitus (requiring treatment)	6 (7)	30 (10)	0.40
Ever smoked	58 (69)	215 (74)	0.41
Current smoking	35 (60)*	130 (60)*	0.99
Aspirin <24 h of AMI	18 (21)	75 (26)	0.39
β blockers	9 (11)	50 (17)	0.15
Ca^{+2} blockers	13 (15)	65 (22)	0.17
Digitalis	0 (0)	4 (1)	0.28
Nitrates	12 (14)	69 (23)	0.07
S_3 sound	1 (1)	11 (4)	0.23
Rales >1/3 lung fields	5 (6)	9 (3)	0.23
Systolic BP on admission (mm Hg)			
Mean ± SD	126.0 ± 21.1	130.8 ± 20.9	0.09
Median (range)	128 (80–178)	130 (86–190)	
Anterior AMI	42 (49)	108 (37)	0.04
Time from pain to therapy (h)			
Mean ± SD	2.7 ± 1.2	3.1 ± 1.4	0.02
Median (range)	2.4 (0.5–5.7)	2.8 (0.3–8.0)	

AMI = acute myocardial infarction, BP = blood pressure.
* Total number value is lower in these categories.

associated with higher creatine kinase release only in anterior wall AMI (adjusted p = 0.03).

Data concerning predischarge MIBI defect size are listed Table III. Infarct size, as assessed by MIBI defect size, was larger in the QRS(+) patients. The same difference was seen when separately analyzing patients with first AMI, patients with prior AMI, anterior, and non–anterior wall AMI. Multivariate regression analysis of patients without prior infarction revealed that after adjustment for baseline variables shown in Table I, QRS(+) pattern continued to be associated with higher predischarge MIBI defect size (adjusted p = 0.03 and 0.02 for anterior and non–anterior wall AMI, respectively).

No difference between the groups was found regarding predischarge left ventricular ejection fraction (Table III).

Coronary angiographic findings: Parallel to the higher rate of anterior wall AMI in the QRS(+) group, the percentage of left anterior descending artery as the infarct-related artery was larger in the QRS(+) group (Table IV). No difference was found between the groups in the rates of 1 or multivessel disease. The rates of patients with 90-minute TIMI flow 0, 1, 2, or 3 were similar between the groups. There was no difference between groups in the collateral score at 90 minutes, nor the presence of visible collaterals in patients with an occluded infarct-related artery.

Clinical outcome: The incidence of either death, reinfarction, severe congestive heart failure, or left ventricular ejection fraction <40%, as was the weighted end point for this combination, tended to be higher in the QRS(+) group (Table V). Progression to Q-wave infarction was seen more often in the QRS(+) group. There was a trend toward increase in 1-year mortality in the QRS(+) group. This difference in mortality outcome was observed only in anterior wall AMI (Table VI). No difference in clinical outcome was seen in non–anterior wall AMI patients. One-year mortality was higher for QRS(+) patients with anterior wall AMI compared with QRS(−) patients.

DISCUSSION

The main findings of this study are that distortion of the terminal portion of the QRS on admission was associated with larger infarct size, as estimated by creatine kinase release over 24 hours and predischarge MIBI defect size. In addition, in anterior wall AMI patients with distortion of the QRS, there was a trend toward increase in the in-hospital weighted end point for mortality, reinfarction, severe heart failure, and left ventricular ejection fraction <40%, and higher rates of 1-year mortality.

A previous study investigating 2,603 patients with AMI[8] found that the in-hospital mortality was significantly higher in QRS(+) patients (6.8%) than in QRS(−) patients (3.8%; p = 0.0008). Multivariate regression analysis showed that the odds ratio for QRS(+) pattern was 1.78 (95% confidence interval 1.19 to 2.68), p = 0.004.[8] The results of our analysis are in accordance with the previous study. The present analysis extends these observations by demonstrating that in addition to short-term prognosis, this simple electrocardiographic sign identifies a subgroup of patients with larger infarct size.

The lack of difference in clinical outcome between the groups of patients with non–anterior AMI may be related to the relative smaller ischemic area at risk of these patients, compared with anterior wall AMI patients. Thus, differences in "severity" of ischemia may not result in absolute large differences in final infarct size and, hence, in prognosis. Moreover, it has recently been shown that in-hospital prognosis in inferior wall AMI is more related to the different patterns of precordial ST depression than to the presence of QRS(+) pattern.[14]

The surface electrocardiogram is a summation of the electrical vectors activating the left ventricle. During severe regional myocardial ischemia the

TABLE II Estimation of Infarct Size by Creatine Kinase in Patients With Versus Without Distortion of the Terminal Portion of the QRS

	QRS (+) Group	QRS (−) Group	p Value
Peak serum creatine kinase (IU)			
Mean ± SD	3,244 ± 2,587	2,299 ± 3,262	<0.001
Median	2,496	1,666	
No.	85	293	
Peak serum creatine kinase for patients with first AMI (IU)			
Mean ± SD	3,189 ± 2,578	2,419 ± 3,490	0.004
Median	2,445	1,780	
No.	78	247	
Peak serum creatine kinase for patients with prior AMI (IU)			
Mean ± SD	3,859 ± 2,817	1,654 ± 1,400	0.04
Median	3,205	1,398	
No.	7	46	
Peak serum creatine kinase (IU) for patient with anterior AMI			
Mean ± SD	4,320 ± 2,932	2,895 ± 4,868	<0.001
Median	3,938.5	2,017	
No.	42	108	
Peak serum creatine kinase (IU) for patients with non–anterior AMI			
Mean ± SD	2,914 ± 1,645	1,950 ± 1,665	0.27
Median	1,942	1,545	
No.	43	185	
Creatine kinase release over 24 h			
Mean ± SD	209 ± 147	155 ± 129	0.003
Median	183	125	
No.	69	249	
Creatine kinase release over 24 h for patients with first AMI			
Mean ± SD	210 ± 149	161 ± 133	0.01
Median	183	137	
No.	63	207	
Creatine kinase release over 24 h for patients with prior AMI			
Median ± SD	198 ± 125	127 ± 108	0.15
Median	214	101	
No.	6	42	
Creatine kinase release over 24 h for patients with anterior AMI			
Mean ± SD	280 ± 168	189 ± 173	0.003
Median	278	160	
No.	31	91	
Creatine kinase release over 24 h for patients with non–anterior AMI			
Mean ± SD	151 ± 95	136 ± 91	0.33
Median	137	120	
No.	38	158	

AMI = acute myocardial infarction.

electrical conduction in the ischemic Purkinje fibers is delayed.[15,16] Thus, the electrical activation of the ischemic zone occurs relatively late. Hence, the terminal vector of the QRS over the ischemic zone is less opposed by activation of the rest of the myocardium. This results in an increase in the R wave in leads in which the terminal vector is directed toward them (terminal R wave) and reduction in the S-wave amplitude in leads recording a complex with a terminal force directed away (terminal S wave).[15–20] Because the Purkinje fibers are less sensitive to ischemia than the contracting myocytes,[21,22] more severe ischemia probably must occur before changes in the QRS configuration are detected.[15,17,23] Disappearance of the S waves in leads with Rs configuration (leads V_1 to V_3) can be easily recognized. In contrast, the absolute R-wave height is influenced by many other variables. Thus, the absolute R-wave amplitude is not helpful in determining the severity of ischemia.

The magnitude of ST elevation is a reflection of the extent of myocardial injury.[24–27] However, because the ST amplitude is influenced by many other factors,[28] absolute measurement of ST amplitudes may not be accurate in estimation of the severity of ischemia. Hence, the second criterion, relating the J point to the R-wave amplitude in leads with qR configuration was constructed to control for the many nonischemic variables influencing absolute ST measurement.

Only a minority of the patients had QRS(+) pattern on admission (Figures 1 to 3).[7,8] It is still unclear what the time course of these changes is, whether the patients who have QRS(−) pattern on admission had developed such QRS changes that had already regressed, or whether this stage had not been reached in the first place.[29] Although in the present study QRS(+) patients were admitted earlier than QRS(−) patients, in the previous study no difference was found in the time elapsed from onset of symptoms to the admission electrocardiogram.[8] The electrocardiographic manifestations of ischemia in patients hospitalized with AMI are reported to be relatively stable, probably owing to the delay from onset of pain.[3,30]

in predischarge left ventricular ejection fraction between the groups may indicate that the ischemic area at risk was comparable.

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TABLE IV Angiographic Findings of Patients With Versus Without Distortion of the Terminal Portion of the QRS

	QRS (+) Group No. (%)	QRS (−) Group No. (%)	p Value
Coronary infarct-related artery			
Left main	0/85 (0)	2/287 (1)	0.02
Left anterior descending	39/85 (46)	99/287 (34)	
Left circumflex	4/85 (5)	51/287 (18)	
Right	42/85 (49)	135/287 (47)	
No. of coronary arteries narrowed >50% in diameter			
1	32/85 (38)	115/287 (40)	0.78
2	33/85 (39)	119/287 (41)	
3	16/85 (19)	43/287 (15)	
4	4/85 (5)	10/287 (3)	
TIMI flow 0 at 90 min	10/83 (12)	47/285 (16)	0.70
TIMI flow 1 at 90 min	5/83 (6)	20/285 (7)	
TIMI flow 2 at 90 min	26/83 (31)	76/285 (27)	
TIMI flow 3 at 90 min	42/83 (51)	142/285 (50)	
Collateral score at 90 min			
0	40/46 (87)	139/170 (82)	0.50
1	6/46 (13)	27/170 (16)	
2	0/46 (0)	4/170 (2)	
Collateral score 1 or 2 (for patients with 90 min TIMI 0–1)	3/9 (33)	12/43 (28)	0.74
% Stenosis at 90 min			
Mean ± SD	79.9 ± 11.5	77.8 ± 15.2	0.19
Median	79.7	77.7	
No.	83	279	

TIMI = Thrombolysis In Myocardial Infarction flow grade.

TABLE V Clinical Outcome of Patients With Versus Without Distortion of the Terminal Portion of the QRS

In-Hospital End Points	QRS (+) Group (n = 85) No. (%)	QRS (−) Group (n = 293) No. (%)	p Value
In-hospital mortality	5 (6)	10 (3)	0.31
Severe CHF/shock	1 (1)	4 (1)	0.89
Recurrent ischemic pain	14 (21)*	59 (28)*	0.26
Reinfarction	5 (6)	16 (5)	0.881
Death/reinfarction/CHF/LVEF <40%	26 (31)	62 (21)	0.070
Weighted end point for death/reinfarction/CHF/LVEF <40% (mean ± SD)	0.21 ± 0.33	0.14 ± 0.28	0.06
Q-wave infarction	62 (74)*	168 (61)*	0.03
1-yr mortality	9 (11)	16 (6)	0.09

CHF = congestive heart failure; LVEF = left ventricular ejection fraction.
* Total number value is lower in these categories.

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TABLE VI Clinical Outcome of Patients With Anterior Wall Acute Myocardial Infarction With Versus Without Distortion of the Terminal Portion of the QRS

In-Hospital End Points	QRS (+) Group n = 42 No. (%)	QRS (−) Group n = 108) No. (%)	p Value
In-hospital mortality	5 (12)	5 (5)	0.11
Death/reinfarction/CHF/LVEF <40%	20 (48)	41 (38)	0.28
Weighted end point for death/reinfarction/CHF/LVEF <40% (mean ± SD)	0.33 ± 0.37	0.24 ± 0.32	0.13
Q-wave infarction	32 (76)	58 (60)	0.06
1-yr mortality	7 (18)	6 (6)	0.03

Abbreviations as in Table V.

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