Four-Year Survival of Patients With Acute Coronary Syndromes Without ST-Segment Elevation and Prognostic Significance of 0.5-mm ST-Segment Depression

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We prospectively evaluated all patients admitted to our coronary care unit during 1993 with ischemic chest pain but without ST-segment elevation on the presenting electrocardiogram, and determined the influence of the extent of ST-segment depression, measured using calipers and blinded to the outcome, on 4-year survival. The presenting symptoms of 367 patients (mean age 64 years) were coded according to the Braunwald classification, 86% being in class IIIB (primary unstable angina with rest angina within 48 hours) and 7.4% in class IIIC (postinfarction angina). Thirty-two patients (8.6%) had myocardial infarction at presentation (defined as a creatine kinase level exceeding twice the reference range within 18 hours). During hospitalization 97% of patients received aspirin, 67% received intravenous heparin, 37% underwent angiography, and 35% underwent revascularization. The vital status of 99% of the patients was determined after a median of 52 months (interquartile range 48 to 55). At follow-up, 88% of patients were taking aspirin, 45% were taking β blockers, and 50% had undergone revascularization. The survival rate was 70% in patients with ≥0.5-mm ST-segment depression (53%, 77%, and 82% survival for ≥2-, 1-, and 0.5-mm ST-segment depression, respectively; p <0.0001). Patients with a normal electrocardiogram had a greater survival rate (94%) than that of patients with 0.5-mm ST-segment depression (82%, p = 0.020), but not significantly different from that of patients with T-wave inversion (84%, p = NS). Independent predictors of mortality (odds ratio [95% confidence interval]) were: age in yearly increments (1.05 [1.03 to 1.06], p = 0.003), revascularization during follow-up (0.40 [0.29 to 0.56], p = 0.006), pulmonary edema (3.45 [2.19 to 5.45], p = 0.007), and ST-segment depression (1.37 [1.20 to 1.55], p = 0.015). Thus, ST-segment depression of ≥0.5 mm predicts 4-year survival in patients with acute ischemic syndromes. ©1999 by Excerpta Medica, Inc.

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Most patients admitted to coronary care units with prolonged ischemic chest pain do not have ST-segment elevation on the presenting electrocardiogram (ECG).[1] Although patients with non–ST-elevation acute coronary syndromes usually have a discharge diagnosis of unstable angina or non–Q-wave myocardial infarction, they represent a continuous spectrum and are often indistinguishable at presentation. The admission ECG provides instant and independent prognostic information. ECG evidence of ST-segment depression (>1 mm) predicts poor early survival.[2,3] The late outcome of patients seen before 1961 has been reported,[4] although there are few recent data available. Patients with marked ST-segment depression (≥2 mm) at presentation are a high-risk group who often present with enzymatic evidence of myocardial infarction,[5–7] are older, have multivessel disease,[8] and have a high 1-year mortality rate.[6,9] This study examines the medium-term survival of unselected patients admitted to a coronary care unit with acute coronary syndromes without ST-segment elevation, and determines the factors predicting prognosis, including the extent of ST-segment depression on the presenting ECG.

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METHODS

In 1993 we prospectively evaluated all patients admitted to the coronary care unit at Green Lane Hospital with prolonged chest pain at rest.[1] Of 642 patients admitted with chest pain, 110 (17%) had myocardial infarction with electrocardiographic evidence of ST-segment elevation or new left bundle branch block,[1] and 152 (24%) had noncardiac chest pain (Figure 1); these patients are not described further in this report.

Clinical management: Creatine kinase measurements were obtained routinely at presentation and 3 times in the next 24 hours, and repeated after any further ischemic episodes. Patients were treated with aspirin, heparin, β blockers, long-acting nitrates, and other antianginal agents, and underwent revascularization as judged appropriate by their physicians. Some

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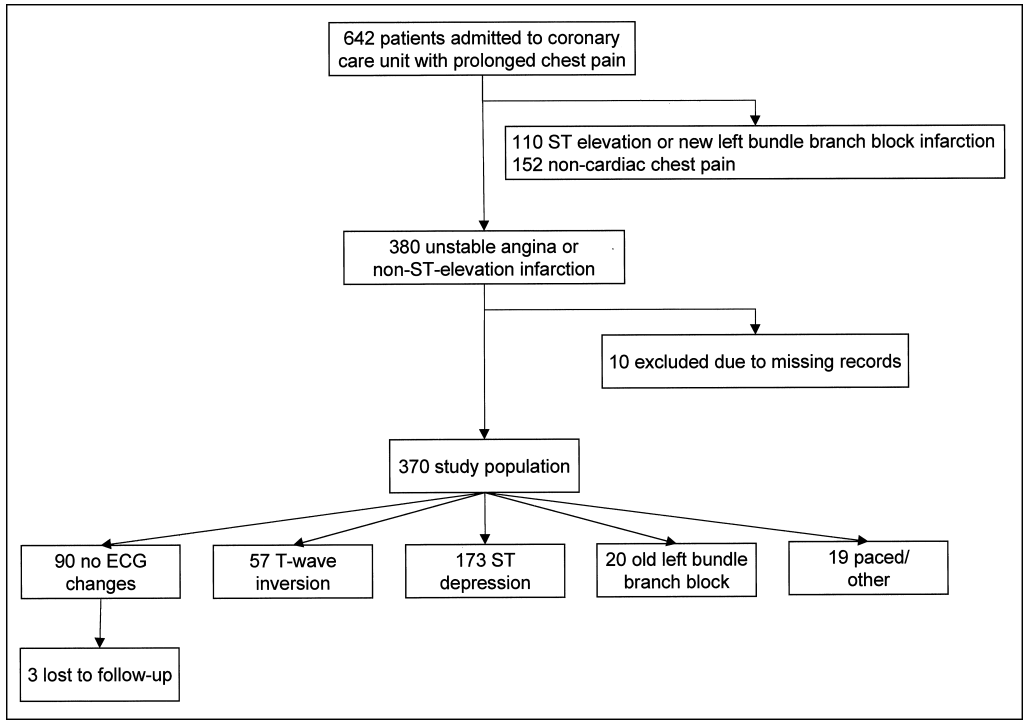

FIGURE 1. Study population.

patients were randomized to receive intravenous heparin or tirofiban.[10]

Electrocardiographic analyses: All patients had an ECG at presentation and at 24 ± 6 hours. Additional ECGs were recorded for recurrent ischemia. ECGs were analyzed blinded to the clinical outcome. ST-segment depression was measured using calipers 80 ms after the J point in intervals of 0.5 mm. T-wave inversion was defined as abnormal if the T-wave deviation was ≥1 mm from the baseline. Patients with ≥0.5-mm ST-segment depression and T-wave inversion were classified as having ST-segment depression. Previously documented left bundle branch block[11] and the location of pathologic Q waves (≥30 ms) were also recorded.

Clinical definitions: At presentation, patients were coded according to the Braunwald unstable angina classification.[12] Patients were diagnosed as having myocardial infarction at presentation if cardiac enzymes exceeded twice the upper limit of the reference range (see later) within 18 hours after admission. Myocardial infarction after presentation was defined as requiring at least 2 of the following: (1) ≥30 minutes of typical ischemic pain; (2) elevation of creatine kinase to >600 IU/L (>2 times the upper limit of the reference range); (3) new Q waves or evolving electrocardiographic changes. Myocardial infarction after coronary artery bypass grafting was defined as the development of new pathologic Q waves in 2 contiguous electrocardiographic leads and/or elevation of aspartate transaminase to ≥100 U/ml.[13] Readmission with unstable angina was defined as hospitalization with ischemic chest pain but without evidence of myocardial infarction. Pulmonary edema on the presenting chest radiograph was recorded. Smoking was defined as current smoking. Hypertension was defined as receiving antihypertensive therapy. Diabetes mellitus was classified according to treatment.

Follow-up: Follow-up was performed by telephoning the patients and their general practitioners to determine vital status, current medical therapy, and risk factors (smoking, hypertension, diabetes, and dyslipidemia). Readmissions were identified by a National Health Index inquiry. Death was classified as either cardiac, vascular, or noncardiovascular.[14] Causes of death or readmission were verified by death certificate, hospital or general practitioner records, or the National Health Index.

Statistical analysis: To examine the relation between the presenting ECG and survival, patients were divided into 4 mutually exclusive groups: ≥0.5-mm ST-segment depression, T-wave inversion, no electrocardiographic changes, or previously documented left bundle branch block. To determine the effect of the extent of ST-segment depression on survival, ST-segment depression was subclassified as 0.5 mm, 1 mm (including 1.5 mm), or ≥2 mm. Categorical variables were compared using the chi-square and Fisher's exact tests (2-tailed). Student's 2-tailed *t* test was used to compare continuous variables. Survival curves were created using the Kaplan-Meier method and compared using the Mantel-Haenszel statistic. Multivariate analysis was performed using stepwise logistic regression in 2 stages, which initially included all factors examined in univariate analysis. Following removal of factors with a log rank p value of >0.5, the final model included age in yearly intervals, the maximum extent

TABLE I Baseline Characteristics According to the Presenting ECG

	All Patients (n = 370)*	No ECG Changes (n = 98)	T-Wave Inversion (n = 57)	≥0.5-mm ST-Segment Depression (n = 173)	LBBB (n = 20)
Age (yrs)	64 (12)	60 (11)	59 (13)	69 (10)†	71 (6)‡
Men	62%	73%	57%	58%	50%
Diabetes mellitus	15%	9%	14%	16%	10%
Cigarette smoking	17%	20%	19%	16%	50%
Systemic hypertension	43%	37%	41%	45%	55%
Prior myocardial infarction	41%	21%	71%	43%†	50%
Prior coronary bypass	15%	12%	18%	13%	25%
Prior coronary angioplasty	14%	17%	25%	8%†	10%
Clinical features					
Pulmonary edema	9.7%	0%	3.6%	16.9%†	10.5%
Infarction at presentation	8.6%	7%	1.6%	19%	0%
Cholesterol (mmol/L)	5.8 (1.2)	5.9 (1.2)	5.4 (1.1)	6.0 (1.2)	5.7 (1)
HDL cholesterol (mmol/L)	1.10 (0.5)	1.03 (0.2)	1.14 (0.8)	1.11 (0.6)	1.13 (0.3)
Peak creatine kinase (IU/L)	222 (354)	257 (419)	163 (190)	342 (485)†	180 (144)

*Includes 19 patients with a missing or paced ECG.
†p = 0.001 for ST-segment depression versus no electrocardiographic changes; ‡p = 0.001 for LBBB versus T-wave inversion and no electrocardiographic changes.
Data are expressed as mean (SD) or percent.
ECG = electrocardiographic; HDL = high-density lipoprotein; LBBB = old left bundle branch block.

TABLE II Outcome According to the Presenting ECG

	All Patients (n = 370)*	No ECG Changes (n = 98)†	T-Wave Inversion (n = 57)	≥0.5-mm ST-Segment Depression (n = 173)	LBBB (n = 20)
Hospital outcome					
Death	5.1%	1.0%	1.8%	7.5%	10%
Infarction	2.2%	2.0%	3.6%	0.6%	5%
Death/infarction	7.0%	3.0%	5.4%	8.1%	15%
1-Year outcome					
Death	13%	3.0%	5.4%	20%‡	25%
Infarction	6.8%	7.1%	8.0%	6.9%	10%
Unstable angina§	29%	30%	42%	24%	35%
Death/infarction	17%	9.0%	12%	22%	25%
Death/infarction/unstable angina§	40%	35%	48%	39%	50%
4-Year outcome					
Death	22%	6.1%	16%	30%‡	45%
Infarction	10%	10%	11%	9.8%	20%
Unstable angina§	42%	41%	54%	39%	35%
Death/infarction	26%	13%	23%	32%‡	50%
Death/infarction/unstable angina§	58%	47%	66%	61%	70%

*Includes 19 patients with a missing or paced ECG.
†Three patients with no electrocardiographic changes were lost to follow-up.
‡p <0.05 compared with no electrocardiographic changes and T-wave inversion.
§Readmission with unstable angina.
Abbreviations as in Table I.

of ST-segment depression, pulmonary edema, diabetes mellitus, previous myocardial infarction, infarction at presentation, in-hospital revascularization, and revascularization at any time during follow-up.

RESULTS

Of the 380 patients with an acute coronary syndrome without ST-segment elevation on the presenting ECG, 10 had insufficient data for analysis (Figure 1). Of the remaining 370 patients, 348 (94%) had experienced chest pain at rest in the preceding 24 hours, 87 (24%) had been transferred from local hospitals, and 27 (7.3%) had had a prior myocardial infarction within 2 weeks. Of the 353 patients with presenting ECGs suitable for analysis, 173 (49%) had ≥0.5-mm ST-segment depression, 57 (16%) had T-wave inversion, 20 (5.7%) had previously documented left bundle branch block, and 101 (28%) had no electrocardiographic changes, (3 were lost to follow-up); the rhythm was paced in 2 patients (Figure 1).

At presentation, 86% of patients were classified as having Braunwald class IIIB unstable angina (23% IIIB1, 49% IIIB2, and 13% IIIB3), and 7.4% class IIIC (postinfarction) angina. Of 98 patients with no electrocardiographic changes, 90% were in class IIIB and 3.1% in class IIIC. Of 173 patients with ≥0.5-mm ST-segment depression, 84% were in class IIIB and

TABLE III Baseline Characteristics and Outcome According to Severity of ST-Segment Depression

	0.5-mm ST-Segment Depression (n = 50)	1-mm ST-Segment Depression (n = 64)	≥2-mm ST-Segment Depression (n = 59)
Baseline characteristics			
Age	62 (12)	67 (12)	71 (8.5)
Men	50%	57%	67%†
Diabetes mellitus	16%	9.4%	19%
Prior infarction	48%	44%	38%
Pulmonary edema	8.2%	13%	29%†
Infarction at presentation	2.1%	6.6%	29%†
Creatine kinase (IU/L)(median [IQR])	85 (67–181)	99 (49–141)	206 (105–773)
Hospital outcome			
Death	2.0%	3.1%	16%
Infarction	0%	6.2%	6.9%
Death/infarction	2.0%	7.7%	24%†
1-Year outcome			
Death	10%	14%	36%
Infarction	2.0%	9.2%	22%
Unstable angina*	30%	23%	20%
Death/infarction	12%	15%	41%
Death/infarction/unstable angina*	32%	34%	49%
4-Year outcome			
Death	18%	23%	47%
Infarction	2.0%	12%	29%
Unstable angina*	50%	38%	31%
Death/infarction	20%	25%	55%
Death/infarction/unstable angina*	62%	57%	68%

*Readmission with unstable angina; †$p < 0.05$ compared with the other 2 categories.
Data are expressed as mean (standard deviation) or percent.
IQR = interquartile range.

6.4% in class IIIC. Of 57 patients with T-wave inversion, 76% were in class IIIB and 21% in class IIIC.

Baseline characteristics: The mean age of patients was 64 years, and 8.6% had infarction at presentation. There were significant differences in baseline characteristics according to the presenting ECG (Table I) and the extent of ST-segment depression (Tables II and III).

Patients with electrocardiographic evidence of any ST-segment depression ≥0.5 mm at presentation were older than those with no electrocardiographic changes or T-wave inversion (69 vs 60 vs 59 years, respectively, $p < 0.001$), and were more likely to have myocardial infarction at presentation or pulmonary edema. Patients with left bundle branch block were also older than those with T-wave inversion or no electrocardiographic changes (71 vs 59 vs 60 years, respectively, $p = 0.001$).

Patients with 0.5-mm ST-segment depression were 5 years younger than those with 1-mm ST-segment depression and 9 years younger than those with ≥2-mm ST-segment depression. They were also more likely to be female or to have myocardial infarction at presentation, and less likely to have pulmonary edema at presentation (all $p < 0.05$, Table III).

Medical treatment: Before admission, 59% of patients were taking aspirin and 50% were taking β blockers. During hospitalization, 97% of patients were given aspirin, 67% intravenous heparin, 71% β blockers, 73% long-acting nitrates, and 61% calcium antagonists; 2.4% of patients were randomized to receive heparin or tirofiban in the Platelet Receptor Inhibition in Ischemic Syndrome Management study.[10] Of the 48 diabetic patients (15% of the total), 44 had type II diabetes (92%), 13 were diet-controlled (27%), 24 were prescribed oral hypoglycemic agents (50%), and 7 required insulin (15%). There were no differences in these treatment rates with respect to electrocardiographic findings at presentation (data not shown).

Hospital outcome: During hospitalization, 18 patients (5.1%) died and 8 patients (2.2%) had an infarction after admission. Angiography was performed in 138 patients (37%), and 129 patients (35%) underwent revascularization, 70 (19%) angioplasty, and 63 (17%) coronary surgery (4 patients had both procedures). Death or myocardial infarction after presentation occurred in 1.4% of patients with no electrocardiographic changes, 2% of those with 0.5-mm ST-segment depression, 7.7% of those with 1-mm ST-segment depression, 24% of those with ≥2-mm ST-segment depression, 20% of those with previously documented left bundle branch block, and 3.2% of those with T-wave inversion (Table III).

Four-year outcome: At median follow-up of 52 months (interquartile range 48 to 55), 80 patients (22%) had died, with 55 deaths being cardiac, 7 vascular, and 18 noncardiovascular. Myocardial infarction after admission occurred in 37 patients (10%), death or myocardial infarction occurred in 100 patients (26%), and 158 patients (42%) were readmitted to the hospital with unstable angina. Revascularization was performed in 184 patients (50%), angioplasty in 89 patients (24%), and coronary surgery in 113 patients (31%). There were no differences in the rates of revascularization according to the presenting ECG. At follow-up, 88% of patients were taking aspirin, 45% β blockers, 31% angiotensin-converting enzyme inhibitors, and 48% lipid-modifying therapy.

The survival rate in patients with ≥0.5-mm ST-segment depression was 70% compared with 84% in those with T-wave inversion and 94% in those without these electrocardiographic changes ($p = 0.0015$). The difference in survival was apparent early in the first year ($p = 0.0004$), with similar event rates occurring in each group after this time (Figure 2). The 4-year survival rate in patients with previously documented left bundle branch block was 55%.

At 1 year, 9% of patients with no ST-segment depression, 12% of those with 0.5-mm ST-segment depression, 15% of those with 1-mm ST-segment de-

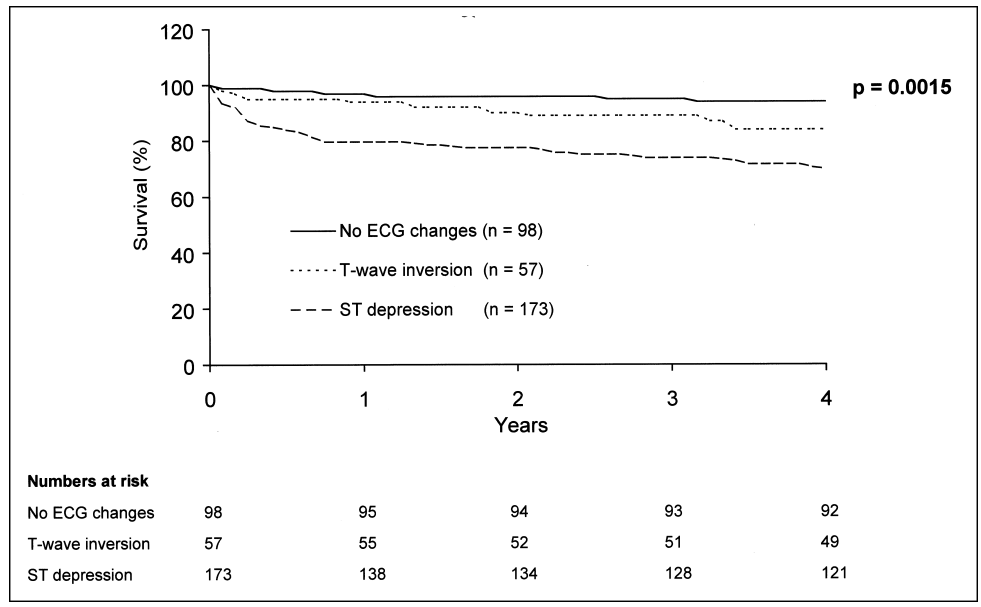

FIGURE 2. Four-year survival according to the presenting ECG. The p values indicated are log-rank comparisons over follow-up.

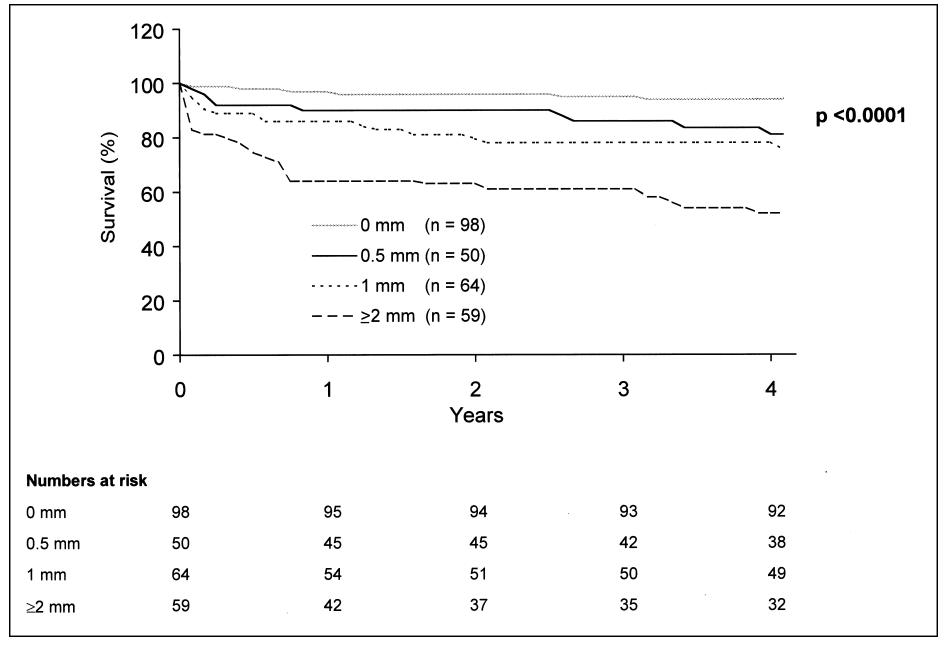

FIGURE 3. Four-year survival according to the severity of ST-segment depression. The p values indicated are log-rank comparisons over follow-up.

pression, 41% of those with ≥2-mm ST-segment depression, and 12% of those with T-wave inversion had died or had a myocardial infarction. There were no differences according to the presenting ECG in the combined end point of death, myocardial infarction, or readmission with unstable angina (Tables II and III).

Severity of ST-segment depression and survival: The 4-year survival rate in patients with ≥2-mm ST-segment depression was 53% compared with 77% in those with 1-mm ST-segment depression, 82% in those with 0.5-mm ST-segment depression, and 94% in those with no electrocardiographic changes ($p < 0.0001$, Figure 3). The difference in survival became apparent in the first year ($p = 0.0016$). The 4-year survival rate in patients with no electrocardiographic changes was 94% compared with 82% in those with 0.5-mm ST-segment depression ($p = 0.020$) and 84% in those with T-wave inversion ($p = 0.057$).

Predictors of 4-year survival: Univariate predictors of 4-year mortality included: age ($p < 0.001$), extent of ST-segment depression ($p < 0.00001$), pulmonary edema ($p < 0.0001$), in-hospital revascularization ($p < 0.001$), revascularization at any time during 4-year follow-up ($p < 0.001$), diabetes ($p = 0.02$), left bundle branch block ($p = 0.02$), previous myocardial infarction ($p = 0.039$), myocardial infarction at presentation

TABLE IV Univariate and Multivariate Predictors of 4-year Mortality

	Odds Ratio (95% CI)	p Value
Univariate Predictors		
Clinical predictors		
Age	–	<0.0001
Diabetes	–	0.02
Previous infarction	–	0.039
Infarction at presentation	–	0.042
Pulmonary edema	–	<0.0001
Revascularization (hospital)	–	<0.001
Revascularization (total)	–	<0.001
ECG predictors		
Maximum ST-segment depression	–	<0.00001
Left bundle branch block	–	0.02
Q waves at presentation	–	0.044
Multivariate Predictors		
Age	1.05 (1.03–1.06)	0.003
Revascularization (total)	0.40 (0.29–0.56)	0.006
Pulmonary edema	3.45 (2.19–5.45)	0.007
Maximum ST-segment depression	1.37 (1.20–1.55)	0.015

($p = 0.042$), and Q waves on the presenting ECG ($p = 0.044$) (Table IV). Multivariate analysis (Table IV) showed that age (odds ratio 1.05, 95% confidence interval [CI] 1.03 to 1.06, $p = 0.003$), total revascularization (odds ratio 0.40, 95% CI 0.29 to 0.56, $p = 0.006$), pulmonary edema (odds ratio 3.45, 95% CI 2.19 to 5.45, $p = 0.007$), and ST-segment depression (odds ratio 1.37, 95% CI 1.20 to 1.55, $p = 0.015$) were independent factors for 4-year mortality. In-hospital revascularization did not predict late survival.

DISCUSSION

This study found that the 4-year survival of patients with unstable angina and non–ST-elevation infarction (93% of whom were in Braunwald class III at presentation) was independently predicted by age, total revascularization, presence of pulmonary edema, and extent of ST-segment depression on the presenting ECG. Importantly, compared with a normal ECG, ≥0.5-mm ST-segment depression adversely influenced 4-year survival.

ST-segment depression and late outcome: Patients with 0.5-mm ST-segment depression had a lower 4-year survival rate than those with no electrocardiographic changes (82% vs 94%, $p = 0.028$). At 1 year there was increased mortality in patients with 0.5-mm ST-segment depression (10% vs 5.4% in patients with T-wave inversion and 3.0% in those with no electrocardiographic changes [$p = 0.200$]).

In the Thrombolysis In Myocardial Infarction III ECG Registry, patients with ST-segment depression had a higher 1-year mortality rate (9.8%) than that of patients with T-wave inversion (5.6%) or no electrocardiographic changes (5.5%).[15] In patients presenting with 0.5-mm ST-segment depression, there was a 16% rate of death or myocardial infarction at 1 year compared with 9.7% in patients with 1-mm ST-segment depression and 15% in those with ≥2-mm ST-segment depression.[15] The survival rates for varying degrees of ST-segment depression were not reported.

In the current study, the 1-year mortality rates of unselected patients with 1- and ≥2-mm ST-segment depressions were 14% and 36%, respectively, compared with 1.5% and 17% in our earlier study that excluded patients aged >76 years,[5] perhaps reflecting the inclusion of elderly patients. Lee et al[6] reported a correlation between increased 1-year mortality and the severity of ST-segment depression in patients aged 68 ± 11 years (29% for ≥2 mm vs 14% for 1-mm ST-segment depression, $p = 0.001$), but the rates of revascularization were not reported.

Two studies have reported the 2- to 4-year outcome of unselected patients presenting with unstable angina. In 1973, Gazes et al[4] reported a mortality rate of 35% at 4 years (mean age 56 years, seen before 1961), and in 1995 Ravkilde et al[16] reported a mortality rate of 25% after 28 months of follow-up in an unselected Danish population (mean age 65 years). The 4-year mortality rate of all our patients (mean age 64) was 22%. In a report describing the 7-year outcome of 282 patients treated for unstable angina in Rotterdam in 1988/1989[17] (two thirds of whom received aspirin, although heparin use was not reported), only 45% of patients had Braunwald class III unstable angina compared with 93% reported here. Age ≥70 years and diabetes were multivariate predictors of late death, whereas electrocardiographic changes (defined as ST-segment depression or elevation of ≥0.1 mm or T-wave inversion of ≥0.1 mV) were not.[17]

Study limitations: Data on ventricular function, the strongest predictor of long-term outcome after myocardial infarction,[14] were not routinely available because only 44% of patients had either an echocardiogram or a left ventriculogram during hospitalization. Although our study prospectively evaluated outcome, the timing of cardiac enzyme tests was not mandated. The reported frequency of myocardial infarction at presentation may have been higher if more frequent blood samples had been taken or if the creatine kinase-MB fraction had been measured routinely. Troponin T and I measurements, which have recently been shown to identify high-risk patients with non–ST-elevation acute coronary syndromes,[2,3] were not routinely available.

Whether patients with non–ST-elevation acute coronary syndromes are managed better with an early invasive or an ischemia-guided strategy is unclear. We found that hospital revascularization did not predict late survival, but revascularization at any time during follow-up did. The randomized Thrombolysis In Myocardial Infarction IIIB[18] and Veterans Affairs Non-Q Wave Infarction Strategies in Hospital[19] studies did not find any mortality benefits at 1 and 3 years, respectively, of an early invasive and/or revascularization strategy compared with an early conservative approach in patients with unstable angina and non–Q-wave myocardial infarction. Also, the Organization to Assess Strategies for Ischemic Syndromes Registry[20] of similar patients did not find any benefit of angiog-

raphy at 6 months. These studies were performed before the use of IIb/IIIa receptor antagonists.[2,21,22]

In the recently presented FRagmin during InStability in Coronary artery disease (FRISC)-II study,[23] patients were randomized after fragmin (dalteparin) therapy for 2 to 6 days to either an invasive strategy, with intervention occurring at a mean of 6 days, or a conservative strategy. The invasive strategy was associated with a 9.5% risk of death in myocardial infarction at 6 months compared with 12% for the conservative strategy ($p < 0.05$). In contrast to earlier studies comparing these strategies, stents were deployed in 61% of percutaneous interventions in the invasive limb. However, further studies are required to evaluate revascularization strategies on therapy background with glycoprotein IIb/IIIa receptor antagonists.

Conclusion: ST-segment depression of 0.5 mm influences 4-year survival, and this electrocardiographic parameter should be incorporated into randomized trials and clinical risk stratification.

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