Usefulness of ST Depression With T-Wave Inversion in Leads V_4 to V_6 for Predicting One-Year Mortality in Non–ST-Elevation Acute Coronary Syndrome (from the Electrocardiographic Analysis of the Global Use of Strategies to Open Occluded Coronary Arteries IIB Trial)

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ST-segment depression (ST-D) on the admission electrocardiogram of patients with non–ST-elevation acute coronary syndromes (NSTEACSs) is associated with higher mortality. However, few studies have evaluated the effect of location of ST-D and T-wave polarity on long-term prognosis of patients with NSTEACS. Electrocardiographic (ECG) and clinical data from 6,770 patients with NSTEACS randomly assigned in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB trial were analyzed retrospectively. One-year mortality was correlated with location of ST-D (leads I and aVL; II, III, and aVF; V_1 to V_3; or V_4 to V_6) and T-wave polarity. ST-D in any of the ECG locations was associated with higher mortality compared with patients without ST-D. Patients with ST-D and T-wave inversion in leads V_4 to V_6 had the highest 1-year mortality rate of all groups (16.2%), significantly higher compared with patients with ST-D without T-wave inversion in those leads (9.0%, $p = 0.001$). Logistic regression analysis showed that age, hyperlipidemia, Killip class >I, history of myocardial infarction, history of heart failure, history of angina pectoris, systolic blood pressure, heart rate, sum of ST-D (odds ratio 1.061, 95% confidence interval 1.035 to 1.087, $p < 0.001$), and ST-D with T-wave inversion in leads V_4 to V_6 (odds ratio 1.374, 95% CI 1.023 to 1.844, $p = 0.035$) were independent predictors of 1-year mortality. Conversely, ST-D without T-wave inversion in leads V_4 to V_6 or other ECG presentations were not independent predictors of high 1-year mortality. In conclusion, ST-D with T-wave inversion in leads V_4 to V_6 on the admission electrocardiogram in patients with NSTEACS identifies those with higher 1-year mortality than for patients with any other ECG presentation. **(Am J Cardiol 2007;99:934–938)**

ST-segment depression (ST-D) on the admission electrocardiogram of patients with non–ST-elevation acute coronary syndromes (NSTEACS) is associated with higher mortality. However, few studies have evaluated the effect of location of ST-D and T-wave polarity on long-term prognosis of patients with NSTEACS. We analyzed the impact of location of ST-D, specifically in leads V_4 to V_6, and polarity of the associated T waves on 1-year mortality in patients with NSTEACS included in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB trial, which included patients with all types of acute coronary syndromes.[1] In the present analysis, we included only patients who presented without persistent ST elevation on the admission electrocardiogram.

Methods

Inclusion criteria to the GUSTO IIB study consisted of chest discomfort within the previous 12 hours associated with either transient ST-segment elevation or depression (>0.5 mm) or persistent definite T-wave inversion >1 mm. Other inclusion and exclusion criteria have been previously reported.[1] We did not exclude patients with electrocardiographic (ECG) confounders because these patients represent a large proportion of patients with ACS (10% of GUSTO IIB patients)[2] and have relatively high mortality.[3] In the present analysis, we included only patients without persistent ST elevation on the admission electrocardiogram who had data for 1-year mortality.

All ECG data were evaluated centrally at the ECG Core Laboratory at Duke Clinical Research Institute. The 12-lead electrocardiogram was recorded at a paper speed of 25 mm/s and sensitivity of 1 mV = 10 mm. ST-D was considered present if the J point was depressed by ≥1 mm and was followed by a horizontal or downsloping ST-D for ≥0.08 seconds in ≥1 of 12 leads, except for lead aVR. Quantitative ST-D in each lead was measured at 1-mm intervals, with every fraction rounded to the nearest whole

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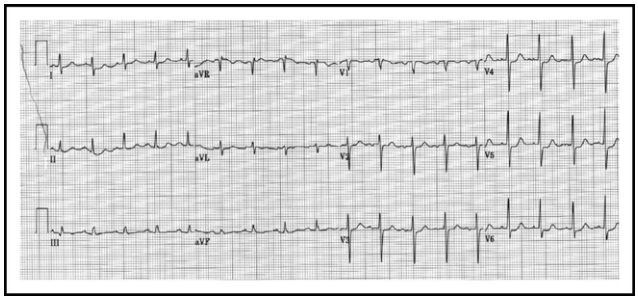

Figure 1. Patient with ST-D and positive T waves in leads V_4 to V_6.

Figure 2. Patient with ST-D and T-wave inversion in leads I, II, and V_4 to V_6.

number. The sum of ST-D was calculated for each patient. ST-D <1 mm was included throughout our analyses in the group with no ST-D. Negative T waves were defined if >50% of the T-wave area was below the isoelectric line.

We compared baseline characteristics and admission ECG patterns of patients who survived 1 year after admission with those of patients who died within the first year. ECG variables included were the sum of ST-D and the presence of ST-D and/or T-wave inversion in each of the 4 groups of leads, with group 1 as leads I and aVL; group 2, leads II, III, and aVF; group 3, leads V_1 to V_3; and group 4, leads V_4 to V_6. In each of the 4 groups of leads, we compared 1-year mortality among patients without ST-D who had positive T waves, those with T-wave inversion without ST-D, those with ST-D without T-wave inversion (Figure 1), and those with ST-D and T-wave inversion (Figure 2). As shown in Figures 1 and 2, patients had to show ST-D or T-wave inversion in all leads in each group. We did not analyze the prognostic significance of ST-D and/or T-wave inversion in the group with >1 lead (e.g., inferolateral leads). We performed logistic regression analysis assessing effects of baseline characteristics, including the mentioned ECG patterns, in each of the 4 groups of leads on 1-year mortality.

Descriptive statistics are summarized as medians with 25th and 75th percentiles for continuous variables, and Kruskal-Wallis test was used for comparisons among groups. For categorical variables, data were summarized as percentages, and the chi-square test was used to assess group differences. Statistical analysis was performed using SPSS (version 13, SPSS Inc., Chicago, Illinois). We consider $p < 0.05$ to be statistically significant. In logistic regression analysis, we included the following parameters: age, gender, current smoking, hypertension, hypercholesterolemia, diabetes mellitus, family history of coronary artery disease, previous angina pectoris, previous myocardial infarction, previous congestive heart failure, previous percutaneous coronary intervention, previous coronary artery bypass graft, systolic and diastolic blood pressure, heart rate, Killip class, sum of ST-D, and pattern of ST-D and T-wave polarity (4 patterns) for each of the 4 groups of leads.

Results

A total of 12,142 patients were enrolled in the GUSTO IIB study; 8,011 of these patients did not have ST elevation or left branch bundle block. Data for 1-year mortality were available for 6,770 patients who were included in our study population. As listed in Table 1, patients who died within 1 year of admission were significantly older and had hypertension significantly more often, diabetes mellitus, previous angina pectoris, previous myocardial infarction, previous coronary artery bypass graft, previous heart failure, lower systolic and diastolic blood pressure, faster heart rate, and higher Killip class on admission. Conversely, current smoking, hyperlipidemia, and family history of coronary artery disease were found significantly less frequently in patients who died.

Patients who died had ST-D in ≥2 leads, higher number of leads with ST-D, and a higher sum of ST-D significantly more often (Table 2). The percentage of patients with ST-D with either positive T waves or T-wave inversion in leads V_4 to V_6 was higher in the group that died.

Overall, patients with ST-D in leads I and aVL had higher 1-year mortality rates (15.5% vs 7.9%, $p < 0.001$) than patients without ST-D in these leads. In addition, patients with T-wave inversion in leads I and aVL had higher mortality rates (13.1% vs 7.6%, $p < 0.001$) than patients without T-wave inversion in these leads. Mortality was highest for patients with both ST-D and T-wave inversion in leads I and aVL (Figure 3); however, it was not different from mortality rates for patients with isolated ST-D in these leads. Mortality of patients with isolated T-wave inversion in leads I and aVL was significantly higher than in patients without ST-D and T-wave inversion in these leads. However, the difference in mortality for those with T-wave inversion in leads I and aVL with and without ST-D was not significant.

One-year mortality rates (14.3% vs 8.1%, $p < 0.001$) were higher for patients with than without ST-D in leads II, III, and aVF. In contrast, the difference in mortality rates (9.8% vs 8.3%, $p = 0.088$) between patients with and without T-wave inversion in these leads was not significant. For patients with ST-D in the inferior leads, mortality was similar between those without and with T-wave inversion (Figure 3). For patients without ST-D in these leads, there was no difference in mortality between patients without and with T-wave inversion. However, mortality was significantly higher for patients with ST-D in leads II, III, and aVF in those without and with T-wave inversion.

ST-D in leads V_1 to V_3 was associated with higher mortality rates (11.5% vs 8.0%, $p = 0.001$). In contrast, T-wave inversion in leads V_1 to V_3 did not affect mortality rates (8.1% vs 8.6%, $p = 0.538$). Mortality was significantly higher for patients with than without ST-D in leads V_1 to V_3 than for those without and with T-wave inversion (Figure

Table 1
Baseline clinical characteristics by survival status at one year

Variable	Alive	Dead	Total	p Value
	(n=6,192, [91.5%])	(n=578 [8.5%])	(n=6,770)	
Age (yrs)*	64.9 (56.1, 72.4)	73.3 (66.7, 79.8)	65.6 (56.9, 73.2)	<0.001
Men	67.2%	63.1%	66.9%	0.052
Current smoker	27.4%	16.1%	26.4%	<0.001
Hypertension	47.6%	53.8%	48.1%	0.005
Dyslipidemia	42.1%	34.4%	41.5%	<0.001
Diabetes mellitus	17.7%	32.4%	18.9%	<0.001
Family history of coronary artery disease	41.3%	33.2%	40.6%	<0.001
Previous angina pectoris	75.2%	84.3%	75.9%	<0.001
Previous myocardial infarction	29.8%	47.8%	31.4%	<0.001
Previous heart failure	5.5%	19.4%	6.7%	<0.001
Previous percutaneous coronary intervention	10.8%	8.5%	10.6%	0.090
Coronary bypass	12.2%	17.8%	12.7%	<0.001
Systolic blood pressure (mm Hg)*	140 (120, 152)	130 (120, 150)	139 (120, 151)	<0.001
Diastolic blood pressure (mm Hg)*	80 (70, 90)	76 (68, 85)	80 (70, 90)	<0.001
Heart rate (beats/min)*	73 (62, 86)	81 (67, 96)	74 (63, 88)	<0.001
Killip class I	88.9%	69.4%	87.2%	<0.001

* Median (25th, 75th percentiles).

Table 2
Prevalence of baseline electrocardiogram variables according to survival status at one year

Variable	Alive	Dead	Total	p Value
	(n=6,192)	(n=578)	(n=6,770)	
ST-D in ≥2 leads	48.2%	66.3%	49.7%	<0.001
No. of leads with ST-D*	0 (0, 3)	3 (0, 5)	0 (0, 3)	<0.001
Sum of ST-D*	0 (0, 4)	3 (0, 8)	0 (0, 5)	<0.001
T-Wave inversion in ≥2 leads	73.7%	69.2%	73.3%	0.021
No. of leads with negative T wave*	0 (0, 3)	0 (0, 3)	0 (0, 3)	0.286
ST-D and negative T wave in leads I and aVL	0.5%	0.7%	0.6%	0.562
ST-D and positive T wave in leads I and aVL	0.8%	1.2%	0.8%	0.231
ST-D and negative T wave in leads II, III, & aVF	0.5%	0.2%	0.5%	0.360
ST-D and positive T wave in leads II, III, & aVF (%)	1.2%	1.7%	1.3%	0.331
ST-D and negative T wave in leads V_1–V_3 (%)	1.0%	0.7%	1.0%	0.658
ST-D and positive T wave in leads V_1–V_3 (%)	2.9%	3.1%	2.9%	0.699
ST-D and negative T wave in leads V_4–V_6 (%)	11.3%	21.5%	12.2%	<0.001
ST-D and positive T wave in leads V_4–V_6 (%)	30.4%	37.7%	31.1%	<0.001

* Median (25th, 75th percentiles).

3). In contrast, T-wave inversion in leads V_1 to V_3 did not affect mortality in the groups without or with ST-D in these leads.

ST-D in leads V_4 to V_6 was associated with higher mortality rates (11.7% vs 6.1%, p <0.001). T-wave inversion in leads V_4 to V_6 was also associated with higher mortality rates (11.8% vs 7.1%, p <0.001) than in the group without T-wave inversion. Mortality was significantly higher in patients with than without ST-D in leads V_4 to V_6 in the groups without and with T-wave inversion in these leads (Figure 3). In contrast, mortality was not affected significantly by T-wave inversion for patients without ST-D in leads V_4 to V_6.

As listed in Table 3, logistic regression analysis shows that age; Killip class >I; history of previous myocardial infarction, heart failure, or angina pectoris; heart rate; sum of ST-D; and ST-D with T-wave inversion in ≥2 leads of V_4 to V_6 with reference to no ST-D and no T-wave inversion in leads V_4 to V_6 were independent predictors of mortality. Isolated T-wave inversion or ST-D with positive T waves in leads V_4 to V_6 and all other groups of ST-D and/or T-wave inversion in the other 3 groups of leads were not independently associated with mortality. Hyperlipidemia and systolic blood pressure were associated with significantly lower mortality.

Discussion

This is the largest analysis of data from a multicenter randomized trial studying the effect of location of ST-D and T-wave polarity on the admission electrocardiogram on 1-year mortality in patients with NSTEACS. On univariate analysis, we found that ST-D, regardless of its location and T-wave polarity, was associated with increased mortality. However, on multivariate analysis, we found that ST-D with T-wave inversion in leads V_4 to V_6 and the sum of ST-D were independent predictors of increased 1-year mortality. Patients presenting with ST-D and T-wave inversion in leads V_4 to V_6 had 1.37 higher odds for 1-year mortality compared with patients without ST-T changes, whereas ST-D and/or T-wave inversion in the other groups of leads

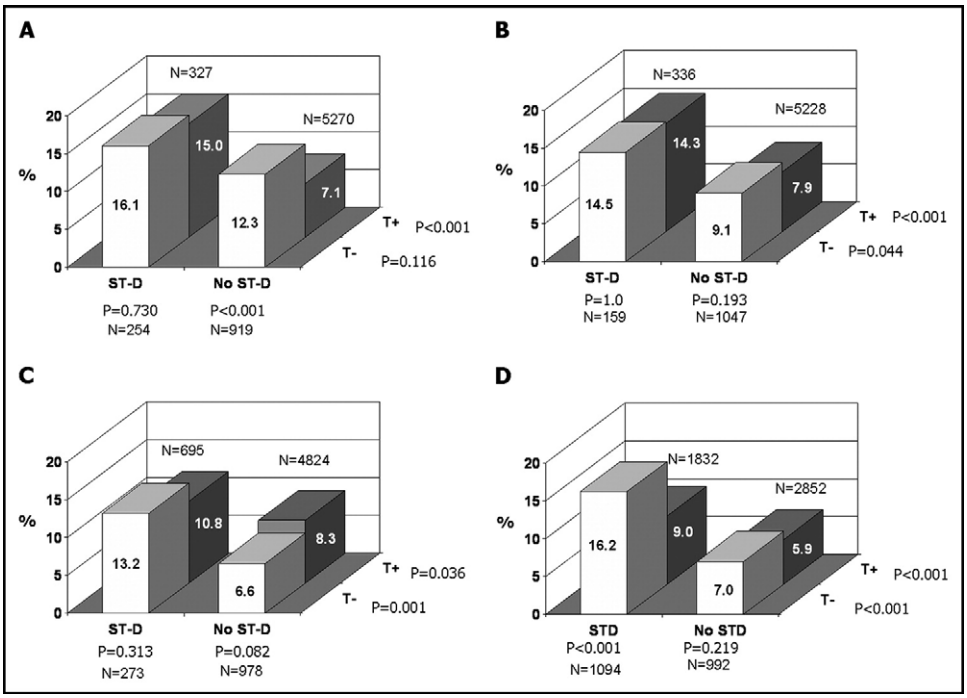

Figure 3. Mortality rates at 1 year according to ST-D and T-wave polarity in the 4 groups of leads. *(A)* For leads I and aVL, mortality is significantly higher in patients with ST-D and positive T waves compared with those without ST-D and significantly higher in those with no ST-D and inverted T waves compared with those with positive T waves. *(B)* For leads II, III, and aVF, the presence of ST-D was associated with significantly higher 1-year mortality regardless of T-wave polarity. *(C)* For leads V_1 to V_3, ST-D in these leads was associated with significantly higher 1-year mortality regardless of T-wave polarity. *(D)* For leads V_4 to V_6, the presence of ST-D in these leads is associated with significantly higher 1-year mortality than no ST-D. ST-D with inverted T waves was associated with the highest mortality, significantly higher than ST-D with positive T waves.

Table 3
Multivariate logistic regression analysis of predictors of one-year mortality

Variable	Odds Ratio	95% Confidence Interval	p Value
Age	1.059	1.049–1.069	<0.001
Hypercholesterolemia	0.795	0.655–0.965	0.021
Diabetes mellitus	1.852	1.512–2.269	<0.001
Previous angina pectoris	1.336	1.037–1.720	0.025
Previous myocardial infarction	1.557	1.283–1.889	<0.001
Heart failure	1.616	1.232–2.119	0.001
Systolic blood pressure	0.989	0.984–0.993	<0.001
Heart rate	1.007	1.002–1.011	0.006
Killip II–IV	1.651	1.321–2.064	<0.001
Sum of ST-D	1.061	1.035–1.087	<0.001
ST-D and T wave in V_4–V_6	1.374	1.023–1.844	0.035

were not independent predictors of outcome. Moreover, just the presence of ST-D with T-wave inversion in leads V_4 to V_6 was a prognostic marker of high mortality regardless of concomitant ECG changes in other lead groups.

Different patterns of ST-D may be associated with distinct coronary anatomy and may signify different risk. Although it is commonly believed that ST-D during tachycardia (i.e., during stress test) cannot be used to localize the ischemic region,[4] it seems that certain patterns of ST-D during spontaneous episodes of ischemia may signify a distinct underlying pathology.

The higher mortality of patients with NSTEACS associated with ST-D in leads V_4 to V_6 may be related to the extent of coronary disease. In inferior wall ST-elevation acute myocardial infarction (STEMI), ST-D in leads I and aVL is a common finding and represents reciprocal changes to the inferior wall ischemia without having prognostic implications. ST-D in aVL may even precede ST elevation in the inferior leads in some patients.[5] However, studies of concomitant ST-D in patients with inferior wall STEMI[6–10] have shown that ST-D in leads V_4 to V_6 was associated with higher mortality[6,7] and higher rates of left anterior descending and/or multivessel coronary artery disease.[8,11] In patients with non-STEMI, the study by Barrabés et al[12] showed that ST-D in ≥2 lateral leads (I, aVL, V_5, and V_6) was associated with lower left ventricular ejection fraction and left main coronary artery or 3-vessel disease more often than in patients without ST-D in the lateral leads. However, the investigators did not differentiate ST-D in leads I and aVL from ST-D in leads V_5 and V_6.

In contrast to ST-D in leads V_4 to V_6, ST-D in leads V_1 to V_3 during inferior wall STEMI may be a sign of posterior wall involvement, and although associated with higher peak serum creatine kinase, it is not associated with increased mortality or multivessel disease.[11] In our population, ST-D in leads V_1 to V_3 was not associated with increased risk.

Our study shows that ST-D with T-wave inversion in leads V_4 to V_6 is associated with significantly higher 1-year mortality than in all other groups. Some studies have shown that T-wave inversion was associated with higher mortality.[13,14] However, these studies did not distinguish between isolated T-wave inversion and that associated with ST-D. Two studies showed that T-wave inversion had no clinical signifi-

cance when it was associated with ST-D.[15,16] In contrast, isolated T-wave inversion without ST-D was associated with adverse outcome.[15–18] Other studies reached contradicting conclusions, showing that isolated T-wave inversion without ST-D was associated with the same[19,20] or even lower mortality than in patients with normal ECG results.[21,22] Mueller et al[22] found that in a 3-year follow-up of 1,450 consecutive patients with unstable angina or non-STEMI, mortality rates were 8% in patients with no ECG changes, 19.9% in patients with ST-D, and only 5.1% in patients with T-wave inversion. After adjustment for potential confounders, ST-D was associated with high mortality (odds ratio 2.2, confidence interval 1.1 to 4.6), whereas T-wave inversion (odds ratio 0.44, confidence interval 0.2 to 0.96) was associated with significantly lower mortality.

This is a retrospective analysis of a randomized prospective multicenter study. However, the large number of patients in each ECG subgroup allowed us to draw conclusions that have statistical significance. Patients with non-STEMI or unstable angina may have transient episodes of ischemia that may not have been detected by the "enrollment" single electrocardiogram. Repeated ECG tracings or continuous ECG monitoring could potentially reveal the pattern and location of ischemic ST-D in patients who did not show ST-D on the admission electrocardiogram. We do not have enzymatic, angiographic, or echocardiographic data that could shed light on the mechanisms of the adverse outcome of patients with ST-D in leads V_4 to V_6. Troponin measurements were not available at the time the study was performed. Such an explanatory study needs to be a prospective multicenter study that will include a large number of patients with non-STEMI or unstable angina. Moreover, the goal of our study is to show that the admission electrocardiogram is a powerful independent predictor of mortality in patients with NSTEACS.

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