Prognostic Significance of ST Segment Shift Early After Resolution of ST Elevation in Patients With Myocardial Infarction Treated With Thrombolytic Therapy: The GUSTO-I ST Segment Monitoring Substudy

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Objectives. We sought to study the relation between recurrent ST segment shift within 6 to 24 h of initial resolution of ST elevation after thrombolytic therapy and 30-day and 1-year mortality.

Background. Rapid and stable resolution of ST segment elevation in relation to thrombolytic therapy in patients with an acute myocardial infarction is an indicator of culprit artery patency. Whether recurrence of ST segment shift during continuous ST monitoring after initial resolution is related to poor prognosis has not been studied.

Methods. ST segment monitoring was performed within 30 min after thrombolytic therapy for acute myocardial infarction. The predictive value of a new ST segment shift (assessed as ≥0.1-mV deviation from the baseline) 6 to 24 h after thrombolytic therapy was studied with respect to 30-day and 1-year mortality.

Results. Of 734 patients, 243 had a new ST segment shift (33%). The 30-day mortality rate in patients with an ST shift (7.8%) was significantly higher than that in patients without an ST shift (2.25%, \( p = 0.001 \)), as was the 1-year mortality rate (10.3% vs. 5.7%, respectively, \( p = 0.025 \)). Multivariable analysis revealed an independent predictive value of ST shift with respect to 30-day mortality (\( p = 0.008 \)), even after consideration of multiple clinical risk factors in the overall Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO)-I mortality model (\( p = 0.0001 \)). Moreover, the duration of the ST shift bore a direct relation with 1-year mortality (\( p = 0.008 \)).

Conclusions. Detection of ST segment shift early after thrombolytic therapy for acute myocardial infarction is a simple, noninvasive means of identifying patients at high risk and is superior to other commonly assessed clinical risk factors. Thus, patients with a new ST shift after the first 6 h, but within 24 h, represent a high risk group that may benefit from more aggressive intervention, whereas patients without evidence of an ST shift represent a low risk subgroup.

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Occluded Coronary Arteries (GUSTO-I) trial (28) and its angiographic substudy (29) showed improved clinical outcomes and angiographic patency in patients treated with an accelerated regimen of alteplase versus streptokinase. The primary goal of the GUSTO-I ST Segment Monitoring Substudy (9) was to provide a noninvasive assessment of the speed and stability of reperfusion. The prognostic significance of recurrent ST shift after initial resolution of ST segment elevation in patients presenting with ST elevation and acute myocardial infarction has not been studied. Thus, we studied the relation between recurrent ST shift 6 to 24 h subacutely after initial resolution of ST elevation after thrombolytic therapy and 30-day and 1-year mortality.

Methods

Patients. The protocol and results of the GUSTO-I trial have been published elsewhere (28). Eligible patients were randomized to receive streptokinase with subcutaneous or intravenous heparin, accelerated alteplase with intravenous heparin or the combination of intravenous alteplase and streptokinase with intravenous heparin.

ST segment monitoring. The details of ST segment monitoring have been reported previously (9,30). We aimed to start ST segment recording within 30 min of thrombolytic treatment and monitoring continued for 24 h. The GUSTO-I ECG Monitoring Substudy was a collaborative effort (30) of three core laboratories, which used one of three ST segment monitoring devices: a three-channel (Frank’s orthogonal X, Y, Z leads) continuous vectorcardiographic monitor (MIDA 1000, Ortivus Medical, Stockholm, Sweden); a 12-lead continuous ECG monitor (ST-100, Mortara Instrument); or a three-channel (bipolar modified V_2, V_5 and aVF leads) Holter monitor (Marquette Electronics). ST segment analysis was first performed in blinded manner as to treatment assignment at the three core laboratories. ECG editing and interpretation were performed by an experienced operator with a computer-assisted device. The technical details of ST segment analysis for the three monitoring devices have been summarized elsewhere (30). The three core laboratories provided edited ST segment trends as a data stream containing the ST segment level at 60 ms after the J point, which was used for this analysis.

We evaluated new ST segment shift after resolution of initial ST elevation within 6 h of thrombolytic therapy (Fig. 1) on the basis of the following criteria: 1) ≥50% resolution of initial ST shift (elevation or depression) in the lead with maximal ST deviation at the initiation of monitoring (6,9) or if maximal ST deviation was not detected, for example, because of the latter hook-up of ST monitoring device, an ST segment level within 6 h of thrombolysis within 0.2 mV (elevation or depression) of zero; otherwise, the resolution of initial ST elevation was not thought to have occurred; 2) duration of ≥50% resolution at ≥10 min within 6 h of thrombolysis; and 3) new ST segment elevation or depression, defined as ≥0.1 mV from the average ST segment baseline >6 h after thrombolysis and lasting ≥1 min. The average ST segment baseline value was calculated from all ST segment data points for the duration of monitoring beyond the initial 6 h. Thus, ST shift as discussed here represents a recurrent ST shift >6 h from the

Figure 1. Average duration of ST shift per hour for all patients from the time of thrombolysis. Vertical lines indicate SD.
time of thrombolytic therapy. Because the duration of monitoring varied among patients, the duration of the ST segment shift for each patient was normalized for 24 h: Normalized duration of ST segment shift = (Actual ST segment shift duration/Hours of monitoring) × 24 h. Total ischemic burden (total ST shift) consisted of ST depression and ST elevation duration. If both ST segment depression and elevation were seen in different leads at the same time, the ST shift with greater ST deviation magnitude was chosen. Excluded from analysis were patients with <12 h of effective monitoring time or a data gap >50% of monitoring time or those in whom recurrence of ST shift could not be assessed. Many patients who underwent continuous ST segment monitoring as part of this substudy also participated in the angiographic substudy (29). ST segment analysis was not performed during coronary angiography to exclude ST segment shift in response to contrast injection or mechanical revascularization.

Statistical analysis. The primary end point was death at 30 days, with a secondary end point of death at 1 year. A comparison of baseline clinical characteristics of patients included in and excluded from this study as well as patients with and without ST segment shift was performed with chi-square test (mean value ± SD for continuous variables). The variable of ST duration was normalized with the logarithmic transformation. The relation between ST segment shift and death was studied with univariate logistical regression analysis. The variable “ST segment shift” was then added to the multivariable model containing the overall 30-day GUSTO-I mortality model (31). One-year survival analysis based on the presence of ST shift was performed with Kaplan-Meier curves. To study the relation between duration of ST shift and death, 30-min increments of ST shift duration were chosen on the basis of previous observations (11,12,14,32).

Results

Patient characteristics. Of 1,067 patients who underwent ST segment monitoring with one of the three devices, 333 were excluded because of a monitoring time <12 h, a data gap duration >50% of monitoring time or other technical difficulties. An additional 41 patients were excluded because resolution of initial ST shift was not achieved. Patients who were excluded from the study (n = 333) were significantly older, more frequently had an anterior myocardial infarction, received thrombolytic therapy later and had a higher mortality rate at 30 days and 1 year than those included in the study. Among 734 patients evaluated in this study, 243 (32%) had an ST segment shift, whereas 491 (67%) patients did not. Among patients with an ST shift, the median duration of the ST shift was 30 min, with 25th and 75th percentiles of 7 and 110 min, respectively; the average duration of the ST shift is shown in Figure 1.

A comparison of baseline clinical and presenting characteristics of patients with and without ST segment shift is shown in Table 1; patients with ST shift were older and more frequently had diabetes mellitus. There was a trend for a more frequent history of anterior infarction and cerebrovascular disease, as well as elevated systolic blood pressure on admission. No differences were seen in the frequency of administration of various thrombolytic regimens or in time to treatment (Table 1).

Recurrent ST segment shift and death. The survival disadvantage in patients with versus those without an ST segment shift can be appreciated early and persists for up to one year (Fig. 2). The mortality rate at 30 days (7.8% vs. 2.25%, odds ratio [OR] 3.7, 95% confidence interval [CI] 1.7 to 7.9, p = 0.008) and at 1 year (10.3% vs. 5.7%, OR 1.9, 95% CI 1.1 to 3.3, p = 0.025) was higher in patients with than those without an ST segment shift, respectively. After adjustment for significant baseline inequalities (Table 1), there continued to be greater mortality in patients with an ST shift at 30 days (p = 0.015).

To further define the prognostic significance of ST segment shift, this variable was added to the overall 30-day GUSTO-I mortality model (31). When ST shift was added to the overall mortality model (OR for the model 2.65, 95% CI 1.9 to 3.7) the duration of the ST shift had an independent and significant incremental value when considered with 1- or 30-min interval increases (OR 1.13, 95% CI 1.03 to 1.24, p = 0.008). To examine whether a continuous relation existed between the duration of the ST shift and 1-year mortality rates, we partitioned the ST shift duration into 30-min intervals. As shown in Figure 3, a good direct relation existed between duration of ST shift and 1-year mortality (r = 0.88, p = 0.008).

Direction of ST segment shift. Among patients with an ST shift, 92 (38%) had ST depression, and 151 (62%) had ST elevation. Compared with patients without an ST shift, there was an increase in the 30-day mortality rate both among those with ST depression (9.78% vs. 2.25%, p = 0.0009, OR 4.71, 95% CI 1.89 to 11.72) and those with ST elevation (6.62% vs. 2.25%, p = 0.012, OR 1.76, 95% CI 1.13 to 2.72). The relation with higher mortality was maintained after adjustment with the GUSTO-I mortality model (31) in patients with ST depression (OR 3.64, 95% CI 1.38 to 9.61, p = 0.009) or ST elevation (OR 2.43, 95% CI 0.96 to 6.12, p = 0.06).

Similarly there was an increase in 1-year mortality rates among patients with ST segment depression compared with those without an ST shift (11.96% vs. 5.7%, p = 0.03, OR 2.25, 95% CI 1.08 to 4.69) and ST elevation (9.3% vs. 5.7%, p = 0.1245, OR 1.30, 95% CI 0.93 to 1.82).

The 30-day prognostic significance of ST depression and elevation persisted after the elimination of two deaths that occurred within the first 24 h.

Discussion

The principal novel finding of this study is that a recurrent ST segment shift detected within 6 to 24 h of thrombolytic therapy and after the initial resolution of ST elevation is an independent predictor of 30-day mortality in patients with an acute myocardial infarction. We also found a direct relation between the duration of the ST shift and 1-year mortality.
Previous studies (16–22) have related poor outcome to recurrent ischemia detected beyond the first day. Our study extends those findings of prognostic significance by demonstrating the importance of early (i.e., within the first 24 h) detection of ischemia when other noninvasive modalities such as stress testing are not applicable and within a time frame in which therapeutic intervention is feasible.

Multiple studies (1–9) have demonstrated that rapid and stable resolution of ST elevation in patients with an acute myocardial infarction is related to patency of an infarct-related artery. Our goal in this respect was to study early risk stratification beyond the initial 6 h when patency status has been established. We were interested in ST segment monitoring beyond this point to identify high risk patients beyond the time frame for immediate intervention, such as rescue angioplasty.

**ST segment elevation.** We observed a higher mortality rate in patients with recurrent ST segment elevation than in those without an ST segment shift; however, the pathophysiology and specificity of ST segment elevation for identifying recurrent ischemia could not be determined from our analysis and remain uncertain. Recurrent ST elevation is thought to reflect a culprit vessel occlusion (6,33–35). Thus, recurrent ST elevation in our analysis may have been indicative of recurrent thrombosis in the infarct-related artery; alternatively, mechanical changes in left ventricular geometry in response to transient alterations in loading conditions, for example, may account for the recurrent ST elevation (6–38).

**ST segment depression.** The pathophysiology of ST segment depression after myocardial infarction is related to the severity of culprit lesion stenosis and the dynamic aspects of the culprit lesion activity, including thrombosis and vasospasm; these result in more frequent recurrent ischemia, persistent left ventricular dysfunction, electrical instability and poor outcome (16,19–22,39). Based on our observations, ST segment depression appears to have a stronger relation to mortality than does ST segment elevation, especially after adjustment for other variables with the GUSTO-I mortality model (31). This may suggest that recurrent ST segment depression is a more specific marker of recurrent ischemia than ST segment elevation.

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<tr>
<th>Table 1. Clinical Characteristics</th>
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<td>No ST Segment Shift</td>
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<td>(n = 491)</td>
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<tr>
<td>Age (yr)*</td>
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<tr>
<td>Male</td>
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<tr>
<td>Other</td>
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<td>Streptokinase+IV heparin</td>
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<td>Streptokinase+SQ heparin</td>
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<tr>
<td>t-PA+streptokinase</td>
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<tr>
<td>Peak creatine kinase-MB (IU/liter)</td>
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*Included in GUSTO-I mortality model (31). Data presented are mean value ± SD or percent of patients. IV = intravenous; SQ = subcutaneous; t-PA = tissue-type plasminogen activator.
Total ischemic burden. We demonstrated the prognostic significance of ST segment depression and ST segment elevation with respect to 30-day or 1-year mortality, suggesting that the measure of overall ST segment shift can be used for prognostic risk stratification, at least when acquired within the first 24 h after acute myocardial infarction. Further insight into the mechanism of our findings would have been provided by concurrent measures of infarct size and ventricular function as well as the status of the culprit vessel.

With acute ischemic syndromes, ST segment shift may be a marker of myocardial ischemia or necrosis depending on the underlying pathophysiology, which can include intracoronary thrombosis, vasoconstriction, distal embolization and microvascular injury. Dynamic changes in ST segments on continuous monitoring have been related to angiographic detection of intracoronary thrombosis (25), cardiac adrenergic dysfunction (26) and thrombus-mediated cycles in coronary flow (27). Thus, ST segment shift represents a convenient surrogate measure of underlying pathophysiology because it is readily available, can be continuously updated, quantitatively relates to the extent of myocardial cell injury in real time and bears a relation to prognosis. The relation of ST segment monitoring to other markers of higher risk patients (40,41) requires further evaluation.

In this era of fiscal restraint and diminishing access to more intense therapy, our findings provide support for the use of this

Figure 2. Kaplan-Meier survival curves for patients with ST shift (dashed line) and those without ST shift (solid line) demonstrating a significant difference in 1-year mortality rates. Overall number of patients available for follow-up at each point in time is also shown.

Figure 3. Relation between duration of ST shift within the first 24 h after myocardial infarction and 1-year mortality rates ($r = 0.88$). Duration of ST shift was grouped on the basis of 30-min intervals and plotted against the respective mortality (average) rate for each group of patients. Significance level is based on univariate analysis of ST shift.
noninvasive and universally available marker of recurrent ischemia for risk stratification. Studies have shown a lack of benefit from the indiscriminate use of target lesion angioplasty in patients early after myocardial infarction (42–51). Our study provides support for the triage of patients with ST shift who represent a high risk group; this increased risk may be mediated by reocclusion of the infarct-related artery or recurrent ischemia. This approach is further supported by the findings of a continuous relation between the duration of ST segment shift and death (Fig. 3) and by the independent predictive nature of ST shift in multivariable analysis, which included the GUSTO-I 30-day mortality model (31).

**Study limitations.** The main limitation of our study relates to the arbitrary selection of a 6 h cutoff period for the detection of recurrent ST shift after thrombolysis. This choice was supported by three considerations: 1) Resolution of the initial ST shift was rapid (Fig. 1), with an apparent “shoulder” at 6 h. 2) Insight from concurrent participation in the angiographic substudy (35) indicated that by 3 h, up to 80% of patients experienced ≥50% resolution of initial maximal ST shift; only a few patients underwent angiography beyond 3 h in the first day (29), precluding further assessment of patency in relation to recurrent ST shift. 3) We wished to study the prognostic significance of ST shift beyond the initial period of thrombolysis and related instability. Approximately one third of patients initially enrolled into this substudy were excluded for technical reasons, which limits the generalizability of our findings. The observation of higher mortality rates in the excluded patients than in the included patients may have resulted in the dilution of the relation between the new ST shift and death. It should also be noted that the relation of ST shift to death was independent of clinical variables and risk factors documented at the time of randomization. However, we did not study ST shift in relation to symptomatic recurrence of ischemia or heart failure or in relation to a particular QRS configuration (e.g., the development of Q waves). Although the accuracy of ST shift detection may have been limited by the use of three different techniques, the concurrence of our findings within each of the technologies facilitates the generalizability of the results.

**Conclusions.** Recurrent ST shift at 6 to 24 h after thrombolytic therapy for acute myocardial infarction is related to increased mortality at 30 days and 1 year. This simple, noninvasive monitoring technique may be of additional prognostic value in the early period after acute myocardial infarction, when rapid decision making pertaining to the management of these patients is required. Patients with a recurrent ST shift within the first 24 h represent a high risk group that may benefit from more aggressive intervention. Patients without a recurrent ST shift represent a low risk subgroup that, in the absence of other high risk features, may be suitable for early discharge.

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