Time to Treatment Influences the Impact of ST-Segment Resolution on One-Year Prognosis

Insights From the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Trial

Yuling Fu, MD; Shaun Goodman, MD; Wei-Ching Chang, PhD; Frans Van de Werf, MD; Christopher B. Granger, MD; Paul W. Armstrong, MD; for the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Trial Investigators

Background—Early ST resolution after reperfusion is a prognostic indicator in acute myocardial infarction. Little information exists regarding the prognostic utility of ST resolution beyond 4 hours after fibrinolysis. Furthermore, the relation between time to treatment, ST resolution at 24 to 36 hours, and 1-year outcome has not been well studied. Accordingly, we undertook a prospective ECG substudy in the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) trial to examine this.

Methods and Results—Patients (n=13,100) were stratified into 3 ST-resolution categories, based on baseline and 24- to 36-hour ECGs: complete resolution (≥70%) in 6698 (51.1%) patients, partial resolution (30% to 70%) in 4610 (35.2%) patients, and no resolution (<30%) in 1792 (13.7%) patients; 1-year mortality rate was 5.1%, 8.0%, and 9.7%, respectively (P<0.001). Among patients treated <2 hours after symptom onset, 55.6% had complete ST resolution, whereas 52.1% and 43% of patients treated between 2 to 4 hours and 4 to 6 hours, respectively, had complete ST resolution (P<0.001). Within each category of ST resolution, patients treated <2 hours had lower 1-year mortality rates as compared with patients treated between 2 to 4 hours or >4 hours (3.8% versus 5.2% and 6.6%, P=0.002 in complete ST resolution; 5.7% versus 8.4% and 9.9%, P=0.001 in partial ST resolution; 7.1% versus 8.7% and 13%, P=0.006 in no resolution). The extent of ST resolution was closely and inversely correlated with 1-year mortality rates (r=−0.963, P<0.001).

Conclusions—ST resolution at 24 to 36 hours after fibrinolysis is influenced by time to treatment and inversely related to 1-year mortality rates. Time to treatment further differentiates between high- and low-risk patients and further highlights the importance of reducing time delay to initiation of fibrinolysis in acute myocardial infarction. (Circulation. 2001; 104:2653-2659.)

Key Words: myocardial infarction ■ fibrinolysis ■ reperfusion
fibrinolytic therapy and the impact of time to treatment on the value of ST resolution in predicting 1-year mortality rates.

Methods

The ASSENT-2 trial has been previously described in detail. Briefly, 16,949 patients were randomly assigned to receive either an accelerated, weight-adjusted infusion of alteplase (≤100 mg) or a single bolus injection of tenecteplase (30 to 50 mg according to body weight) if they had onset of symptoms of AMI within 6 hours before random assignment and had no protocol-specified contraindications to enrollment. ECG criteria for admission were ST-segment elevation ≥0.1 mV in at least two limb leads or ≥0.2 mV in two contiguous precordial leads or the presence of left bundle-branch block.

The ASSENT-2 ECG substudy consisted of the entire ASSENT-2 study population (16,949 patients) from 1021 hospitals and prespecified that a 12-lead ECG be recorded at baseline and 24 to 36 hours after fibrinolysis. The ST-segment measurement was evaluated centrally without reader knowledge of the treatment assignment or clinical outcome at the ECG Core Laboratories (Canadian VIGOUR Center, University of Alberta, Edmonton and Canadian Heart Research Center, Toronto). The overall interobserver agreement between ECG readers was 93.4%, indicating very good concordance between ECG readers. To minimize confounding factors that might influence the accuracy of assessment of ST-segment elevation, patients were excluded from this analysis if they had one of the following: (1) left bundle-branch block, paced rhythm, ventricular rhythm, poor-quality ECG at either baseline or 24 to 36 hours; (2) in-hospital reinfarction before a 24- to 36-hour ECG was obtained; and (3) missing baseline or 24- to 36-hour ECG. The final ECG substudy group consisted of 13,100 patients (Figure 1).

ECG Analysis

The amount of ST-segment elevation was measured manually 20 ms after the J point with the use of a hand-held caliper. The sum of ST-segment elevation was measured from leads I and aVL and V1 to V6 for anterior myocardial infarction and leads II, III, aVF, V5, and V6 for inferior myocardial infarction. The resolution of ST-segment elevation at 24 to 36 hours was stratified into 3 categories, based on Schröder’s method3,4: Complete resolution was defined as resolution of the initial sum of ST-segment elevation ≥70%; partial resolution was defined as ST-segment resolution <70% to 30%, and no resolution was defined as ST-segment resolution <30%.

Statistical Analysis

Descriptive statistics were summarized as medians with 25th and 75th percentiles for continuous variables, and the Kruskal-Wallis test was used for comparisons of 3 categories of ST-segment resolution. For categorical variables, the data were summarized in percentages, and Fisher’s exact test or the χ² test was used to assess group differences. Kaplan-Meier survival estimates and the Cox proportional hazards regression model were used to compare time to the first occurrence of the end points between the groups. One-year mortality data are 92.3% complete.

A univariate analysis was first performed to identify important baseline characteristics associated with mortality rates at 1 year. Variables examined included age, sex, presence of hypertension or diabetes, current smoking, previous myocardial infarction, previous CABG, systolic and diastolic blood pressures, heart rate, location of infarction, Killip class, time from symptom onset to treatment, and treatment assigned. Multivariate logistic and Cox proportional hazards regression models were developed through the use of backward, stepwise variable selection procedures to assess the effect of baseline characteristics and ECG variables on 1-year mortality rates. Adjusted 1-year mortality rate was calculated by adjusting key baseline characteristics with the logistic regression. The overall performance of the models was assessed in terms of the C-index (or the area under a receiver operator characteristic curve). All tests were 2-sided, with a 5% level of significance. All analyses were performed with the use of SPSS (Version 10.07).

Results

Overall, 13,100 patients were stratified into the 3 conventional ST-resolution categories: Complete (≥70%) resolution was present in 6698 (51.1%) patients, partial (30% to 70%) resolution in 4610 (35.2%) patients, and no resolution (<30%) in 1792 (13.7%) patients on the ECG recorded 24 to 36 hours after fibrinolytic therapy. The baseline characteristics and clinical events according to the categories of ST resolution are depicted in the Table. A higher percentage of patients in the complete ST-resolution group were women and current smokers. Patients with a history of diabetes, previous myocardial infarction, and prior CABG as well as those with Killip class >1 were more likely to have partial or no ST resolution (all P<0.002). Patients with anterior infarction were also more likely to have no or partial ST resolution than patients with a non-anterior myocardial infarction. A significantly higher percentage of patients with partial (71%) and no resolution (62%) had peak creatine kinase MB level ≥5 times above the upper limit of normal as compared with patients with complete ST resolution (59%, P<0.001). Analysis of clinical outcomes revealed that shock, congestive heart failure, and recurrent angina and ischemia all occurred more often in patients with partial or no ST resolution (Table).

The median (25th and 75th percentiles) time interval from treatment to the acquisition of 24- to 36-hour ECGs for the categories with complete, partial, and no ST resolution was 27.1 (24.7, 33.8), 26.7 (24.5, 32.3), and 26.9 (24.5, 33.4) hours, respectively. As seen in the Table, time to treatment was significantly shorter among patients who had complete resolution. The extent of ST resolution became significantly less with increasing time to treatment (Figure 2A). Among patients treated within 2 hours after symptom onset, 55.6% had complete ST resolution, whereas 52.1% and 43% of patients treated between 2 to 4 hours and 4 to 6 hours, respectively, had complete ST resolution (P<0.001). The
extent of ST resolution by distribution of presenting infarction over the three time point periods is shown in Figure 2B. As would be expected, anterior infarcts were less likely to show ST resolution than were non-anterior infarcts at each of the three time points. It was also noteworthy that among patients who were treated 2 hours, 2 to 4 hours, and 4 hours, peak creatine kinase MB levels 5 times above the upper limit of normal were 61%, 65%, and 66%, respectively (P<0.001).

Kaplan-Meier survival curves for the complete, partial, and no ST resolution groups are depicted in Figure 3. Highly significant differences in mortality rates were evident early and persisted to 1 year among the three ST-resolution categories (P<0.001 for all pairwise comparisons by the log rank test). These differences in mortality rates remained significant even after adjusting for key baseline characteristics (shown in Figure 4) such as age, history of previous myocardial infarction and hypertension, infarct location, Killip class, systolic blood pressure, heart rate, and time to treatment. The adjusted relative risk of death at 1 year among patients with partial versus those with complete ST resolution was 1.46 (95% CI, 1.23 to 1.72); among patients with no resolution versus those with complete ST resolution, adjusted relative risk was 1.72 (95% CI, 1.40 to 2.10). The only significant interaction was between age and Killip class. The C-index values for the 1-year mortality model was 0.79, reflecting good discriminatory and predictive power.

Figure 5 shows 1-year mortality rates according to the extent of ST resolution and time to treatment. Overall, 1-year mortality rates for complete, partial, and no resolution were 5.1%, 8.0%, and 9.7%, respectively. Within each category of ST resolution, patients who were treated earlier (2 hours) had lower 1-year mortality rates as compared with patients treated between 2 to 4 hours or those treated beyond 4 hours (3.8% versus 5.2% and 6.6%, P<0.001 in the complete ST resolution group; 5.7% versus 8.4% and 9.9%, P=0.001 in the partial ST resolution group; 7.1% versus 8.7% and 13%, P=0.006 in the no resolution group). Within each time-to-treatment window, comparisons of mortality rates of patients in different ST-resolution categories revealed that patients with complete ST-segment resolution had the lowest 1-year mortality rates as compared with those with partial or no resolution (3.8%, 5.7%, and 7.1%, P=0.003 for patients treated within 2 hours after onset of symptoms; 5.2%, 8.4%, and 8.7%, P<0.001 for those treated within 2 to 4 hours; 6.6%, 9.9%, and 13%, P<0.001 for those treated between 4

| Baseline Characteristics and Clinical Outcomes According to ST-Segment Resolution Category |
|-----------------------------------------------|----------------|----------------|
| Complete Resolution  | Partial Resolution | No Resolution  |   |
| (n=6698)            | (n=4610)        | (n=1792)        |   |
| Age, y              | 61 (52–70)      | 62 (52–70)      | 60 (51–70)      | 0.021 |
| Age ≥75             | 10.6            | 12.3            | 11.3            | 0.020 |
| Female sex          | 23.4            | 21              | 18.1            | <0.001 |
| Hypertension        | 37              | 38.8            | 37.8            | 0.169 |
| Diabetes            | 13.5            | 16.7            | 21.2            | <0.001 |
| Previous myocardial infarction | 14.2          | 15.9            | 17.9            | <0.001 |
| Prior CABG          | 3.2             | 3.8             | 4.9             | 0.002 |
| Current smoking     | 48.7            | 42.6            | 41.6            | <0.001 |
| Anterior myocardial infarction | 26.4          | 51.2            | 52.1            | <0.001 |
| Heart rate, bpm     | 72 (60–84)      | 73 (63–85)      | 74 (64–86)      | <0.001 |
| Systolic blood pressure | 132 (118–150)  | 135 (120–150)   | 135 (120–150)   | <0.001 |
| Killip class ≥1     | 9.6             | 11.7            | 13              | <0.001 |
| Time to treatment, hr | 2.6 (1.8, 3.6) | 2.8 (1.9, 4.0)  | 3.0 (2.1, 4.4)  | <0.001 |
| Peak creatine kinase MB ≥5 UNL | 59            | 71              | 62              | <0.001 |
| Time to peak creatine kinase MB, hr | 11.3 (6.5, 14.9) | 10.6 (6.4, 15.4) | 11.5 (6.4, 16.7) | 0.079 |
| Patients with time to peak creatine kinase MB <12 hr | 55            | 55              | 48              | <0.001 |
| Clinical outcomes   |                 |                 |                 |   |
| Shock               | 1.6             | 3.1             | 4.5             | <0.001 |
| Stroke              | 0.7             | 0.6             | 1.1             | 0.126 |
| CHF                 | 5.3             | 8.8             | 11.3            | <0.001 |
| Re-ischemia         | 24              | 25.3            | 27.6            | 0.007 |
| Reinfarction        | 3.7             | 3.3             | 3.9             | 0.377 |
| Death               |                 |                 |                 |   |
| In hospital         | 2.0             | 3.4             | 5.3             | <0.001 |
| At 30 d             | 2.5             | 4.1             | 6.3             | <0.001 |
| At 1 y              | 5.1             | 8.0             | 9.7             | <0.001 |

Values are given as percentages or medians (25th, 75th percentiles). UNL indicates upper normal limit.
to 6 hours). It is noteworthy that 1-year absolute mortality rate was 0.9% lower in patients with partial resolution but treated within 2 hours than that of patients with complete ST resolution but treated beyond 4 hours.

Figure 2. A, Distribution of ST-segment resolution according to time to treatment, \( P<0.001 \) for trend comparison. B, Comparisons of extent of ST resolution over 3 time periods according to infarct locations, \( P<0.001 \) for both anterior and non-anterior myocardial infarction locations.

Figure 3. Kaplan-Meier survival curves for patients with complete resolution, partial resolution, and no resolution determined 24 to 36 hours after fibrinolytic therapy. Log rank test shows \( P=0.018 \) for comparison between partial resolution and no resolution. All other pairwise comparisons between ST-resolution categories are statistically significant at \( P<0.0001 \).

Figure 4. Relative risk for 1-year death by adjusted Cox regression analysis.

Adjusted versus actual 1-year mortality rates are depicted in Figure 6, according to the extent of ST resolution and time to treatment. Actual mortality rates among all patients who had complete ST resolution and as well as those with partial ST resolution treated <2 hours were lower than the adjusted rates. However, the actual mortality rates were higher than the adjusted rates for patients with no resolution and those with partial resolution treated beyond 2 hours. The standardized mortality ratios (the ratio of actual and adjusted mortality rates) with 95% CI for complete, partial, and no ST resolution were 0.82 (CI=0.73 to 0.91), 1.12 (CI=0.99 to 1.25), and 1.34 (CI=1.14 to 1.53), respectively.

To best demonstrate the relation between ST resolution and mortality rates, the data are plotted in progressive declining 10% changes in ST resolution (Figure 7). The extent of ST resolution was closely and inversely correlated with 1-year mortality rates (\( r=0.963, P<0.001 \)).

Discussion

The principal novel finding of this study was that ST-segment resolution determined at 24 to 36 hours after the initiation of fibrinolytic therapy is a strong and independent predictor of 1-year mortality rates in patients with AMI. Indeed, the extent of ST-segment resolution is inversely related in a linear fashion to 1-year mortality rates. Furthermore, our study demonstrates that incorporating time to treatment provided additional prognostic value beyond that of ST resolution in discriminating individual patients with lower 1-year rates. This underscores the importance of achieving early reperfusion to reduce subsequent mortality rates.

Studies on myocardial contrast echocardiography and PET have demonstrated that inadequate myocardial tissue perfusion is associated with poor recovery of regional and global left ventricular function. Successful epicardial reperfusion but persistent ST elevation is associated with reduced left ventricular function and increased mortality rates. Recent data suggest that ST-segment resolution as a continuous physiological maker of myocardial reperfusion predicts out-
comes better than the simultaneously acquired TIMI flow grade of the infarct-related artery. The extent of early ST resolution as a prognostic indicator has been addressed in previous studies. The assessment of early ST resolution could assist clinicians in the early identification of high-risk patients eligible for immediate intervention, such as rescue angioplasty. However, the predictive value of this early single assessment is limited by instability of ST-segment evolution after fibrinolysis. Schroder has recently reported that there was substantial crossover among three categories of ST-segment resolution assessed at both 90-minute and 180-minute ECGs. Hence, among 220 patients with complete ST resolution at 90 minutes, 7% deteriorated to partial or no ST resolution at 180 minutes. By contrast, of 374 patients with no ST resolution at 90 minutes, 21% improved to complete and 46% to partial ST resolution at 180 minutes. Schroder’s study suggested that the patients in the high-risk group appear to be best characterized by no resolution at 180 minutes rather than 90 minutes.

In the study by Kwon et al., 12-lead-ECGs were continuously monitored for 571±326 minutes in 31 patients at 10-minute intervals. They demonstrated lability in the ST segments, with frequent episodes of recurrent ST elevation, both symptomatic and silent, in the first 24 hours after infarction. More than 50% of patients with early resolution had either transient or sustained (median, 43 minutes) recurrences of ST elevation. Sustained recurrent ST elevation was associated with reduced late coronary artery patency and

Figure 5. One-year mortality rates by degree of ST-segment resolution status according to time to treatment (P=0.002 for comparison of mortality rates within complete ST resolution group and within partial ST resolution group, P=0.006 for comparison within no ST resolution group).

Figure 6. Adjusted vs actual 1-year mortality rates according to extent of ST resolution and time to treatment. Among patients who had complete ST resolution and patients with partial ST resolution but treated <2 hours, actual mortality rates were lower than adjusted rates. However, actual mortality rates were higher than adjusted rates for patients with no resolution and patients with partial resolution but treated beyond 2 hours.

Figure 7. ST resolution partitioned into 10% intervals and its relation with 1-year mortality rates (r=-0.963, P<0.001).
worse residual stenosis at 7- to 10-day angiography after thrombolysis.\textsuperscript{18} In a study by Dissmann et al.,\textsuperscript{19} 81 patients with AMI underwent 24-hour Holter monitoring of the infarct-related ST-segment elevation at the initiation of thrombolytic therapy; among 67 patients with ST resolution during the first 4 hours, 46% had subsequent reelevation, with 26% having recurrent changes within the first 4 hours. Patients with recurrence of ST-segment elevation had more in-hospital reinfarction (26% versus 6%, \textit{P}=0.04) than those without. These patients also had a higher rate of occluded infarct-related vessels at angiography assessed 9±4 days after infarction than those without (40% versus 17%, \textit{P}=0.01). An ST-segment monitoring study from Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) I also showed that 98% of study patients had 50% recovery of ST-segment elevation within the first 24 hours,\textsuperscript{20} and ST reelevation 6 to 24 hours after fibrinolysis predicted worse outcome.\textsuperscript{21} Thus, a single early assessment of ST resolution could fail to identify high-risk patients with recurrent ST elevation since the median time to the first transient recurrence of ST elevation was 2.5 hours and the median time to sustained reocclusion was 5.5 hours.\textsuperscript{18} The underlying cause of ST reelevation has been shown to be related to transient or sustained reocclusion\textsuperscript{18,22} or evolution of repolarization abnormalities in areas of infarction.\textsuperscript{23} Thus, assessment of ST resolution at 24 to 36 hours has an important prognostic utility beyond the initial period of thrombolysis and related instability.

Complete ST resolution at 24 to 36 hours among 51% of our study population indicates good 1-year survival, with a 1-year mortality rate of 5.1%. However, the mortality rate for the 13% of patients with no ST resolution was nearly double (9.7%) this rate. Incorporating time to treatment can further discriminate individual patients with a favorable outcome from those with a poor one within each category of ST resolution. After adjustment for differences in baseline characteristics, the risk of death was lowest in patients with complete ST resolution and patients with partial resolution treated within 2 hours (the risk of 1-year death was reduced by 1%, ranging from 1.4% to 0.3%). The risk of death increased in patients with no ST resolution and those with partial ST resolution treated >2 hours (the risk of death was increased by 1.8%, ranging from 4.6% to 0.9%).

One possible explanation for our findings is a greater extent of early myocardial salvage as the result of a shorter time to treatment. Reimer and colleagues\textsuperscript{24} study in an animal model showed that the final infarct size is very sensitive to the duration of ischemia before reperfusion, with little salvage of myocardium realized if reperfusion is accomplished >2 hours after coronary occlusion. The ischemia time to recanализation also affects the severity of microvascular damage assessed with \textsuperscript{99m}Tc-macroaggregated albumin scintigraphy.\textsuperscript{25} Raitt and colleagues\textsuperscript{26} have studied the myocardium area at risk in patients with ST-elevation myocardial infarction before treatment and final infarct size by using \textsuperscript{201}TI and found that there was a progressive decline in the extent of myocardium salvaged as the interval between symptoms and therapy increased. With each 30-minute increase in symptom duration before thrombolytic therapy, there was an associated increase in infarct size of 1% of the myocardium. In our study, a shorter time to treatment was associated with more complete ST resolution. These patients proved to be a very low-risk group potentially suitable for early discharge. High-risk patients appear to be best characterized as those treated beyond 2 hours after symptom onset with partial or no resolution 24 to 36 hours after fibrinolysis. These patients tended to have a higher peak creatine kinase MB level (>5X). Treatment that improves myocardial (microvascular) reperfusion might have enhanced their survival.\textsuperscript{27} A significant difference in the extent of ST resolution was noted in our study between current-smoker patients and those nonsmokers in favor of current smokers. This supports the Second Thrombolytic Trial of Eminase in Acute Myocardial Infarction (TEAM-2) findings with regard to early patency and patient smoking status and may represent a greater initial thrombotic burden.\textsuperscript{28}

Our study has some limitations. First, patients who did not have a second ECG after 24 to 36 hours after fibrinolytic therapy were excluded from this analysis. Second, patients with ECG confounding factors and patients with reinfarction before the second ECG were excluded. Both limit this analysis to an overall lower-risk population. Notwithstanding these limitations, the study group included 77% of the entire study population and hence applies to the large majority of this cohort.

The clinical implications of our findings as related to patient treatment are unclear, but given the high morbidity and mortality rates associated with failure to resolve ST elevation at 24 to 36 hours, a more aggressive diagnostic and therapeutic strategy could potentially improve patient outcomes in this subset. Additionally, it is noteworthy that the outcomes of patients with ST resolution at 24 to 36 hours are similar to those previously reported from patients with early resolution of the ST segment, that is, 90 or 180 minutes. The relative prognostic utility of these measurements at different points in time is unknown and deserving of future study.

Conclusions
The extent of ST-segment resolution determined at 24 to 36 hours after fibrinolytic therapy is influenced by the time to treatment and inversely related to 1-year mortality rates. This evaluation is inexpensive, noninvasive, and easily repeated as compared with other measures such as nuclear imaging and angiography, which require more time to acquire, complex facilities, and greater expense. Incorporating time to treatment further differentiates between a high-risk and a low-risk group of patients. These results further highlight the importance of reducing the time delay between symptom onset and the initiation of fibrinolytic therapy in patients with AMI.

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References

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