ST-Elevation Acute Coronary Syndromes in the Platelet Inhibition and Patient Outcomes (PLATO) Trial: Insights From the ECG Substudy

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Background—Ticagrelor, when compared with clopidogrel, reduced the 12-month risk of vascular death/myocardial infarction and stroke in patients with ST-elevation acute coronary syndromes intended to undergo primary percutaneous coronary intervention in the PLATelet inhibition and patient Outcomes (PLATO) trial. This prespecified ECG substudy explored whether ticagrelor’s association with vascular death and myocardial infarction within 1 year would be amplified by (1) the extent of baseline ST shift and (2) subsequently associated with fewer residual ST changes at hospital discharge.

Methods and Results—ECGs were evaluated centrally in a core laboratory in 3122 ticagrelor- and 3084 clopidogrel-assigned patients having at least 1 mm ST-elevation in 2 contiguous leads as identified by site investigators on the qualifying ECG. Patients with greater ST-segment shift at baseline had higher rates of vascular death/myocardial infarction within 1 year. Among those who also had an ECG at hospital discharge (n=4798), patients with ≥50% ST-deviation (ST-dev) resolution had higher event-free survival than those with incomplete resolution (6.4% versus 8.8%, adjusted hazard ratio 0.69 (0.54–0.88), P=0.003). The extent of ST-dev resolution was similar irrespective of treatment assignment. The benefit of ticagrelor versus clopidogrel on clinical events was consistent irrespective of the extent of baseline ST-dev (P(interaction)=0.728). When stratified according to conventional times from symptom onset, ie, ≤3 hours, 3 to 6 hours, >6 hours, the extent of baseline ST-dev declined progressively over time. As time from symptom onset increased beyond 3 hours, the benefit of ticagrelor appeared to be more pronounced; however, the interaction between time and treatment was not significant (P=0.175).

Conclusions—Ticagrelor did not modify ST-dev resolution at discharge nor was its benefit affected by the extent of baseline ST-dev. These hypothesis-generating observations suggest that the main effects of ticagrelor may not relate to the rapidity or the completeness of acute reperfusion, but rather the prevention of recurrent vascular events by more powerful platelet inhibition or other mechanisms.


Key Words: myocardial infarction ▪ electrocardiography ▪ angioplasty ▪ thrombosis ▪ platelets

The PLATelet inhibition and patient Outcomes (PLATO) study demonstrated that, in comparison with clopidogrel, the reversibly binding oral P2Y12 receptor antagonist ticagrelor reduced the 12-month risk of death resulting from vascular causes, myocardial infarction (MI), or stroke in a spectrum of both non–ST-elevation acute coronary syndromes (non-ST-E ACS) as well as ST-E ACS patients intended to undergo primary percutaneous coronary intervention (PCI).1 A prespecified analysis of the ST-elevation (ST-E) PLATO cohort patients subsequently confirmed that the effects of ticagrelor were consistent with the results in the overall trial; it was noted, however, that this ST-E cohort was somewhat heterogeneous, and that the majority of clinical benefit was obtained during the long term.2,3

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Given that the window of randomization for ST-E patients in PLATO was temporally broad, ie, within 24 hours of...
symptom onset, a prespecified ECG substudy was undertaken to help characterize these patients. This study explored the hypotheses that the treatment effect of ticagrelor on vascular death and MI would be (1) amplified by the extent of baseline ECG abnormalities, and (2) associated with less residual ST change at hospital discharge. Secondarily, we evaluated the impact of temporal delay between symptom onset and commencement of therapy on outcomes and whether the extent of baseline ST-segment shift contributed to the likelihood of adverse cardiovascular outcomes, namely vascular death and recurrent MI.

Methods

Patients with ST-E ACS were enrolled in PLATO if primary PCI was planned, and were required to have at least 1 mm of ST-E in 2 contiguous leads or left bundle branch block as identified by investigators on their qualifying local ECG. Among 6410 ST-E patients’ ECGs analyzed, 204 patients were identified as having left bundle branch block by the core laboratory and were excluded from this analysis. Hence, the final substudy cohort consisted of 3122 patients assigned to ticagrelor and 3084 patients assigned to clopidogrel.

ECG Analysis

ECGs were evaluated centrally at the ECG Core Laboratory (Canadian VIGOUR Centre, Edmonton, Canada) without knowledge of treatment assignment, procedural results, or clinical outcomes. ST-E was measured at the J point with magnified calipers to the nearest 0.05 mV. ST-segment depression was also measured at the J point by similar methods. The sum total ΣST-deviation (ΣST-dev) across all leads, with the exception of aVR, was used to determine either ST-E sums (ΣST-E) or ST-depression sums. The percent resolution of ΣST-E or ΣST-dev from baseline to discharge was dichotomized in accordance with the European Society of Cardiology and American College of Cardiology/American Heart Association guidelines into either ≥50% or <50%.5,6

Statistical Analysis

Categorical variables were summarized by the use of percentages, and continuous variables were reported as medians with 25th and 75th percentiles. Differences between groups were tested by χ² for categorical variables and nonparametric tests (ie, Wilcoxon rank sum or Kruskal-Wallis tests) for continuous variables. Time from symptom onset to randomization was considered as a categorical variable with both 3- and 6-hour cut points within the 24-hour window from symptom onset in accordance with American College of Cardiology/American Heart Association STEMI Guidelines and clinical performance measures.5,6

Assessment of ΣST-E and ΣST-dev were considered as categorical and continuous variables with respect to their associations with cardiovascular death or re-MI within 1 year. The relationships among ECG, metrics, and/or study treatment on the end points were examined by the use of Kaplan-Meier survival analysis with pairwise comparisons based on the log-rank test. To account for imbalance in other patient characteristics, these associations were adjusted for age, heart rate, systolic blood pressure, Killip class, and index MI location as assessed by the ECG Core Laboratory in Cox proportional hazard regression models.7 Restricted cubic spline functions and 5 knots were used to examine the linearity assumption, graphically and statistically, of the continuous variables such as ECG metrics and time from symptom onset.8,9 The associations between ΣST resolution and the end point were evaluated in patients who were event-free at discharge. Unadjusted and adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) generated by Cox proportional hazard regression models were reported. Several interactions were evaluated: study treatment and ECG metrics, study treatment and time from symptom onset, and ECG metrics and time from symptom onset.

| Table 1. Selected Patient Characteristics of the ST-E Patients According to Study Treatment |
|---------------------------------------------|-----------------|-----------------|
|                                             | Ticagrelor      | Clopidogrel     |
| n                                           | 3122            | 3084            |
| Age, y                                      | 59 (52–68)      | 59 (52–68)      |
| Female                                      |                 |                 |
| ≥75 y                                       | 352 (11.3)      | 353 (11.5)      |
| BMI, kg/m²                                   | 27.3 (24.7–30.1)| 27.2 (24.6–30.1)|
| Habitual smoker                              | 1435 (46.0)     | 1401 (45.4)     |
| Hypertension                                | 1854 (59.4)     | 1783 (57.8)     |
| Dyslipidemia                                | 1236 (39.6)     | 1206 (39.1)     |
| Diabetes mellitus                           | 602 (19.3)      | 641 (20.8)      |
| Prior MI                                     | 394 (12.6)      | 392 (12.7)      |
| Prior PCI                                    | 265 (8.5)       | 233 (7.6)       |
| Prior coronary artery bypass graft           | 71 (2.3)        | 66 (2.1)        |
| Prior nonhemorrhagic stroke                  | 85 (2.7)        | 97 (3.2)        |
| Peripheral arterial disease                 | 142 (4.6)       | 131 (4.3)       |
| Congestive heart failure                     | 86 (2.8)        | 74 (2.4)        |
| Chronic obstructive pulmonary disease        | 138 (4.4)       | 129 (4.2)       |
| Creatinine clearance, mL/min                 | 85.8 (68.1–103.7)| 85.9 (67.5–104.3)|
| Heart rate, beats per minute                 | 75 (66–86)      | 75 (66–87)      |
| Systolic blood pressure, mm Hg               | 131 (120–150)   | 130 (120–150)   |
| Diastolic blood pressure, mm Hg              | 80 (70–90)      | 80 (70–90)      |
| Positive troponin I at entry                 | 2660 (86.8)     | 2657 (88.0)     |
| Killip class >2                              | 25 (0.8)        | 33 (1.1)        |

Continuous variables presented as median (25th, 75th percentile); categorical variables presented as n(%). BMI indicates body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Results

As in the overall trial, the treatment groups were well balanced in the ECG ST-E cohort with respect to their baseline characteristics (Table 1). In Table 2, key temporal relationships and ECG metrics are shown according to study treatment. The interquartile ranges of time from symptom onset to relevant trial metrics were broad and consistent with the wide randomization window of 24 hours in the PLATO trial. The median time from symptom onset to baseline ECG, to randomization, and to PCI (5 hours), and from first dose of study drug to PCI, as well, were well balanced between treatment groups. The site of infarction was also similar, as was the extent of ΣST-E and ΣST-dev on the baseline ECG.

In the bottom of Table 2, those patients who had both baseline and discharge ECGs are shown. The median interval between these 2 sets of ECG observations was 3 days and similar in both treatment groups. Resolution of both ΣST-E and ΣST-dev was substantial and comparable between treatment groups, with approximately two-thirds of the overall population achieving at least 50% resolution of their initial baseline ST shift.

All tests were 2-sided with a 5% level of significance. All analyses were performed with the use of SAS version 9.2 (Cary, NC).
Associations Among $\Delta ST$-dev, Study Treatment, and 1-Year Vascular Death/MI

Similar to the primary PLATO results, ticagrelor-assigned patients were less likely to experience MI or vascular death within the first year (7.2% versus 9.8%; HR 0.80, 95%CI [0.67–0.95], P=0.013). This benefit of ticagrelor versus clopidogrel on clinical events within the first year was more pronounced. However, the interaction between time and treatment with clopidogrel occurred in 52.4% of patients and was equally balanced between treatment groups. The ECG findings were not modulated by prerandomization treatment with clopidogrel.

**Associations With Time From Symptom Onset**
To explore the impact of time from symptom onset, the data were partitioned according to conventional time windows, ie, ≤3 hours, 3 to 6 hours, and >6 hours (Table 3). The extent of baseline $\Delta ST$-E and $\Delta ST$-dev declined progressively with each treatment over these time intervals ($P<0.001$ for both). In the paired-ECG cohort, the extent of $\Delta ST$-dev resolution also declined with time especially after 6 hours ($P<0.001$). With longer times from symptom onset to randomization, there was a progressive rise in the composite of vascular death/MI, and each of the individual components, as well (Table 3; $P<0.001$ for all). In Figure 2 (top), the relationship between study treatment and time from symptom onset on outcome is shown. Whereas there appeared to be little difference evident in treatment effect among patients treated early, ie, <3 hours, as time from symptom onset to randomization increased to between 3 and 6 hours, and especially >6 hours, the benefit of ticagrelor over clopidogrel appeared more pronounced. However, the interaction between time and treatment was not statistically significant ($P[interaction]=0.175$; Figure 2). When time from symptom onset was examined further as a dichotomous variable with the use of a 3-hour conventional cut point, a similar pattern favoring ticagrelor over clopidogrel emerged (Table 4). Although those patients randomly assigned after 3 hours showed a significant treatment association with the use of ticagrelor (HR 0.77, 95%CI [0.63–0.93], the test for interaction was not significant ($P=0.156$; Figure 2).

The association between time from symptom onset and 1-year vascular death/MI was also not modified by the extent of $\Delta ST$-dev resolution (Figure 1, bottom), patients assigned to ticagrelor with complete $\Delta ST$-dev resolution had improved event-free survival in comparison with those assigned to clopidogrel (HR 0.66, 95%CI [0.49–0.88]), whereas the treatments appeared similar in those with incomplete $\Delta ST$-dev resolution. However, the interaction term for these findings was not statistically significant ($P[interaction]=0.134$). Prerandomization treatment with clopidogrel occurred in 52.4% of patients and was equally balanced between treatment groups. The ECG findings were not modulated by prerandomization treatment with clopidogrel.
of baseline \( \Delta ST\)-dev or resolution at discharge (\( P \)\{interaction\}=0.656; 0.594, respectively; Figure 2, bottom). In the bottom of Table 4, a similar pattern was evident for those patients with paired observations at baseline and hospital discharge, with no differences between ticagrelor and clopidogrel evident on the extent of \( \Delta ST\)-dev resolution. In the online-only Supplemental Materials, analyses based on time from symptom onset as a continuous variable are reported.

Associations of \( \Delta ST\)-dev with 1-Year Vascular Death/MI

Finally, to assess the relationship between the extent of baseline ST shift and clinical outcomes, we assessed the association between 1-mm increases in ST-segment shift. This association was more pronounced in those patients who had greater baseline \( \Delta ST\)-dev (<5 mm: HR 0.98, 95%CI [0.96–1.00], \( P \)=0.066; \( \geq \)5 mm: HR 1.03, 95%CI [1.01–1.05], \( P \)=0.003) and similarly those with \( \Delta ST\)-E (<3.5 mm: HR 0.97, 95%CI [0.94–1.00], \( P \)=0.044; \( \geq \)3.5 mm: HR 1.02, 95%CI [1.00–1.03], \( P \)=0.133). After adjusting for key baseline characteristics, only baseline \( \Delta ST\)-dev remained significantly associated with clinical outcomes (\( \Delta ST\)-dev <5 mm: HR 0.98, 95%CI [0.96–1.00], \( P \)=0.070; \( \geq \)5 mm: HR 1.02, 95%CI [1.00–1.04], \( P \)=0.016). In the 4798 patients who had a second ECG at hospital discharge, we examined the association between \( \Delta ST\)-dev resolution and vascular death/MI (Table 3). The Kaplan-Meier estimates of 1-year vascular death/MI were compared across treatment groups and time from symptom onset, with no differences between treatment groups. Continuous variables presented as median (25th, 75th percentile); categorical variables presented as \( n(\% \) ). Differences in continuous ECG metrics were tested by the Wilcoxon rank sum test; in categorical ECG metrics by the \( \chi^2 \) test; and in KM% by the log-rank test. MI indicates myocardial infarction; \( \Delta ST\)-E, \( \Delta ST\)-elevation; \( \Delta ST\)-dev, \( \Delta ST\)-deviation; KM%, Kaplan-Meier estimates of event rates. *\( P \)<0.05 (between study treatments).

### Table 3. ECG Metrics and Kaplan-Meier Estimates of Vascular Death/MI According to Time From Symptom Onset and Study Treatment

<table>
<thead>
<tr>
<th>Symptom to Randomization</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>920</td>
<td>908</td>
<td>951</td>
<td>936</td>
<td>1251</td>
<td>1240</td>
</tr>
<tr>
<td><strong>Baseline ( \Delta ST)-E, mm</strong></td>
<td>7.0 (4.0–12.0)</td>
<td>6.5 (4.0–11.5)</td>
<td>5.5 (3.0–10.5)</td>
<td>6.5 (3.0–11.5)*</td>
<td>3.5 (2.0–7.0)</td>
<td>3.5 (2.0–7.0)</td>
</tr>
<tr>
<td><strong>Baseline ( \Delta ST)-dev, mm</strong></td>
<td>12.0 (7.5–18.0)</td>
<td>11.0 (7.0–17.5)</td>
<td>10.0 (5.5–15.5)</td>
<td>11.0 (6.5–17.5)*</td>
<td>7.0 (3.5–11.5)</td>
<td>6.5 (3.5–11.0)</td>
</tr>
<tr>
<td><strong>1-y vascular death/MI, KM%</strong></td>
<td>6.8</td>
<td>6.7</td>
<td>6.4</td>
<td>7.5</td>
<td>9.6</td>
<td>13.0*</td>
</tr>
<tr>
<td><strong>Vascular death, KM%</strong></td>
<td>3.5</td>
<td>2.7</td>
<td>3.6</td>
<td>4.5</td>
<td>4.9</td>
<td>7.2*</td>
</tr>
<tr>
<td><strong>MI, KM%</strong></td>
<td>3.7</td>
<td>4.3</td>
<td>3.4</td>
<td>5.4*</td>
<td>6.0</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Paired cohort, n</strong></td>
<td>726</td>
<td>708</td>
<td>725</td>
<td>715</td>
<td>964</td>
<td>960</td>
</tr>
<tr>
<td><strong>( \Delta ST)-E</strong></td>
<td><strong>6.5 (4.0–11.5)</strong></td>
<td><strong>6.5 (3.0–11.5)</strong></td>
<td><strong>6.5 (3.0–11.5)</strong></td>
<td><strong>6.5 (3.0–11.5)</strong></td>
<td><strong>6.5 (3.0–11.5)</strong></td>
<td><strong>6.5 (3.0–11.5)</strong></td>
</tr>
<tr>
<td><strong>( \Delta ST)-dev</strong></td>
<td><strong>7.0 (7.0–17.5)</strong></td>
<td><strong>7.0 (7.0–17.5)</strong></td>
<td><strong>7.0 (7.0–17.5)</strong></td>
<td><strong>7.0 (7.0–17.5)</strong></td>
<td><strong>7.0 (7.0–17.5)</strong></td>
<td><strong>7.0 (7.0–17.5)</strong></td>
</tr>
<tr>
<td><strong>Resolution ( \geq )50%</strong></td>
<td><strong>560 (77.1)</strong></td>
<td><strong>547 (77.3)</strong></td>
<td><strong>510 (70.3)</strong></td>
<td><strong>504 (70.5)</strong></td>
<td><strong>500 (51.9)</strong></td>
<td><strong>484 (50.4)</strong></td>
</tr>
<tr>
<td><strong>Vascular death/MI, KM%</strong></td>
<td>6.2</td>
<td>6.2</td>
<td>6.4</td>
<td>8.1</td>
<td>9.5</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Vascular death, KM%</strong></td>
<td>6.2</td>
<td>6.2</td>
<td>6.4</td>
<td>8.1</td>
<td>9.5</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>MI, KM%</strong></td>
<td>4.0</td>
<td>4.6</td>
<td>3.4</td>
<td>5.6*</td>
<td>6.3</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Continuous variables presented as median (25th, 75th percentile); categorical variables presented as \( n(\% \) ). Differences in continuous ECG metrics were tested by the Wilcoxon rank sum test; in categorical ECG metrics by the \( \chi^2 \) test; and in KM% by the log-rank test. MI indicates myocardial infarction; \( \Delta ST\)-E, \( \Delta ST\)-elevation; \( \Delta ST\)-dev, \( \Delta ST\)-deviation; KM%, Kaplan-Meier estimates of event rates. *\( P \)<0.05 (between study treatments).
death/MI within 1 year. As evident in Figure 3, patients with ≥50% resolution had a significantly better event-free survival than those with incomplete resolution (6.4% versus 8.8%; HR 0.69, 95%CI [0.56–0.87], P=0.001). This association remained significant after adjustment (≥50% versus <50%: adjusted HR 0.69, 95%CI [0.54–0.88], P=0.003). In Figure 4 the association between ST-dev resolution and treatment assignment on vascular death/MI within 1 year is shown. As noted previously, those patients assigned to ticagrelor with complete ST-dev resolution had better event-free survival, but the interaction term for this finding was nonsignificant.

**Discussion**

Our evaluation of ST-E patients with core ECG data from the PLATO study provides several novel insights. The extent of ST-dev present at the time of randomization proved to be independently associated with vascular death
and MI within 1 year. Furthermore, no treatment effect of ticagrelor versus clopidogrel was evident on the resolution of the initial baseline $\Delta$ST-dev at the conclusion of the 3-day interval between admission and hospital discharge. However, in comparison with clopidogrel, there was a tendency for ticagrelor to provide greater benefit among those patients who achieved the greatest resolution of $\Delta$ST-dev at hospital discharge. Coupled with the previously demonstrated, more pronounced clinical benefit from ticagrelor in ST-E patients after the initial 24 hours of treatment in PLATO, this finding may signal that those patients with more myocardium preservation (as denoted by greater $\Delta$ST-dev resolution) are also those at increased risk of secondary vascular events, and hence amenable to more intense platelet inhibition therapy.3 To achieve this augmentation, for example, on reducing stent thrombosis without an increase in major bleeding is consistent with later benefit and less ischemia.1 Another mechanism of benefit could relate to inhibition of adenosine uptake by red blood cells favorably influencing myocardial perfusion.10 Finally, at least one-quarter of PLATO patients had impaired kidney function, a subpopulation in which clopidogrel is known not to be of benefit.11

It is noteworthy that the magnitude of baseline $\Delta$ST-E and $\Delta$ST-dev we observed in the current investigation is considerably less than in previous studies involving both fibrinolytic and primary PCI12–14; this probably reflects the later benefit and less ischemia. Another mechanism of the initial baseline $\Delta$ST-E and $\Delta$ST-dev. This probably reflects spontaneous resolution of ST changes over time, and the potential impact of surveillance bias associated with the inclusion or exclusion of sicker patients, as well. On the other hand, there was a progressive increase in vascular death and re-MI associated with later randomization and PCI; this may relate to reduced effectiveness from reperfusion in STEMI patients known to occur with treatment delay and supported by the lesser $\Delta$ST-dev resolution during the later time window.14,15 In a previous analysis of ST-E patients in PLATO, no difference in treatment effect was noted when time from symptom onset was examined according to a 12-hour partitioning.3 However, in the current study, when examining narrower time windows from symptom onset, we observed a trend toward progressive augmentation of the effect of ticagrelor in patients treated beyond 3 hours. Although plausible, this trend remains a hypothesis-generating observation given that the interaction test did not achieve statistical significance.

Our study has both strengths and limitations that deserve comment. Because not all ST-E PLATO patients were included in our study, the results could be subject to selection bias. However, the baseline characteristics of the excluded patients were similar, and this selection bias seems unlikely.3 Although we observed amplification of the benefit of ticagrelor in patients treated later after symptom onset and in those with greater $\Delta$ST-dev resolution at hospital discharge, these findings did not achieve statistical significance when tested for interaction, and, hence, we cannot exclude the play of chance, and thus these findings must be considered hypothesis-generating. The $\Delta$ST-dev resolution data are subject to potential bias because they were acquired in the smaller population (n=4798) who survived to 3 days after admission. We cannot preclude a different result had the ECG data been acquired earlier after study therapy was commenced, and, thus, further studies in a more typical, earlier presenting STEMI population may be warranted. However, the ECG data were analyzed in an experienced core laboratory, and the impact of $\Delta$ST-dev resolution on prognosis is in accord with both fibrinolytic and primary PCI-treated patients from other studies in this laboratory.13,16

Given the current findings in a well defined ST-E cohort and those of the primary study, it seems likely that ticagrelor plays a particularly important role in those
patients with extensive territory at risk as manifested by their admission ECG findings. Although we cannot exclude an early effect of ticagrelor, the absence of an effect on ST resolution in the current population suggests that the main effects may not relate to the rapidity of acute reperfusion, but rather that additional beneficial effects may be at play, such as prevention of recurrent vascular events known to modulate long-term outcomes. This hypothesis is supported by the previously demonstrated favorable effects on recurrent MI, ischemia, and stent thrombosis in the ST-E PLATO population without a commensurate increase in bleeding.3

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References


**CLINICAL PERSPECTIVE**

In a prespecified analysis of 6311 ST-elevation patients in the PLATElet inhibition and patient Outcomes (PLATO) study, we explored whether ticagrelor’s treatment effect would be amplified by the extent of baseline ECG abnormalities and associated with less residual ST change at discharge. The extent of $\Sigma$ST-deviation present at the time of randomization was independently associated with 1-year vascular death and myocardial infarction. The benefit of ticagrelor versus clopidogrel was consistent irrespective of the extent of baseline $\Sigma$ST-deviation and no treatment effect of ticagrelor versus clopidogrel was evident on the resolution of baseline ST-deviation at hospital discharge. As compared with clopidogrel, ticagrelor tended to provide greater benefit amongst those patients who achieved the greatest resolution of ST-deviation at discharge. These data suggest that the main effects of ticagrelor may not relate to the rapidity of acute reperfusion but rather prevention of recurrent vascular events known to modulate long term outcomes.
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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL RESULTS

*Time from symptom onset to randomization as a continuous variable*

Time from symptom onset to randomization was considered in the analyses as a continuous variable in addition to the categorical approach presented in the manuscript. In Figure A1, the log HR plot for vascular death/MI within one year indicates the non-linearity of time from symptom onset (Linearity test: p=0.253).

SUPPLEMENTAL FIGURE 1.
When the relationship of the study treatment and vascular death/MI within one-year was examined, there was no evidence that time from symptom onset modulated the association (Figure A2, p(interaction)=0.556), similar to that reported in Figure 2 of the corresponding manuscript.

SUPPLEMENTAL FIGURE 2.
The relationship of the $\Sigma$ST-dev with vascular death/MI within one-year did not appear to be influenced by increasing time from symptom onset (Figure A3, $p$(interaction)=0.368), similar to that reported in Figure 2 of the corresponding manuscript. Similar observations were made regarding the resolution of $\Sigma$ST-dev (Figure A4, $p$(interaction)=0.815).

SUPPLEMENTAL FIGURE 3.

![Graph showing the relationship between time from symptom onset to randomization and HR for $\Sigma$ST-D<5mm vs ≥5mm.](image)

SUPPLEMENTAL FIGURE 4.

![Graph showing the relationship between time from symptom onset to randomization and HR for $\Sigma$ST-D res <50% vs ≥50%.](image)