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.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00391872.

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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). 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 $\Sigma$ST-deviation ($\Sigma$ST-dev) across all leads, with the exception of aVR, was used to determine either ST-E sums ($\Sigma$ST-E) or ST-depression sums. The percent resolution of $\Sigma$ST-E or $\Sigma$ST-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 $\geq$50% or $<$50%.4,5

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 using $\chi^2$ 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. As in the overall trial, the treatment groups were well balanced regarding clinical performance measures.5,6

Assessment of $\Sigma$ST-E and $\Sigma$ST-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 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. Asymmetry in ST-segment deviations (ST-dev) across all leads 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 $\Sigma$ST-deviation ($\Sigma$ST-dev) across all leads, with the exception of aVR, was used to determine either ST-E sums ($\Sigma$ST-E) or ST-depression sums. The percent resolution of $\Sigma$ST-E or $\Sigma$ST-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 $\geq$50% or $<$50%.4,5

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 $\Sigma$ST-E and $\Sigma$ST-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 $\Sigma$ST-E and $\Sigma$ST-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.
The association between time from symptom onset and 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]=0.013; 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 baseline ST-deviation; MI, myocardial infarction; HR, hazard ratio.

Figure 1. Associations between study treatment and vascular death/MI within 1 year according to baseline ST-dev and resolution at discharge.

*HRs were adjusted for age, heart rate, systolic blood pressure, Killip class, and MI location. ST-D and ST-dev indicate ST-deviation; MI, myocardial infarction; HR, hazard ratio.
of baseline $\triangle$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 $\triangle$ST-dev resolution. In the online-only Supplemental Materials, analyses based on time from symptom onset as a continuous variable are reported.

### Associations of $\triangle$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 $\triangle$ST-dev ($\geq 5$ mm: HR $0.98$, 95%CI $[0.96–1.00]$, $P = 0.066$; $\leq 5$ mm: HR $1.03$, 95%CI $[1.01–1.05]$, $P = 0.003$) and similarly those with $\triangle$ST-E ($\geq 3.5$ mm: HR $0.97$, 95%CI $[0.94–1.00]$, $P = 0.044$; $\leq 3.5$ mm: HR $1.02$, 95%CI $[1.00–1.03]$, $P = 0.133$). After adjusting for key baseline characteristics, only baseline $\triangle$ST-dev remained significantly associated with clinical outcomes ($\triangle$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 $\triangle$ST-dev resolution and vascular death/MI.
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/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.

**Table 4. ECG Metrics and Kaplan-Meier Estimates of Vascular Death/MI According to Time From Symptom Onset (3-h Cut Point) and Study Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Symptom to Randomization ≤3 h</th>
<th>Symptom to Randomization &gt;3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ticagrelor</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-E, mm</td>
<td>7.0 (4.0–12.0)</td>
<td>6.5 (4.0–11.5)</td>
</tr>
<tr>
<td>ST-dev, mm</td>
<td>12.0 (7.5–18.0)</td>
<td>11.0 (7.0–17.5)</td>
</tr>
<tr>
<td><strong>Vascular death/MI, KM%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-y vascular death/MI</td>
<td>6.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Vascular death, KM%</td>
<td>3.5</td>
<td>2.7</td>
</tr>
<tr>
<td>MI, KM%</td>
<td>3.7</td>
<td>4.3</td>
</tr>
<tr>
<td><strong>Resolution ≥50%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm</td>
<td>7.0 (4.0–12.0)</td>
<td>7.0 (4.0–11.5)</td>
</tr>
<tr>
<td>Discharge, mm</td>
<td>1.5 (0.5–3.5)</td>
<td>1.5 (0.5–3.5)</td>
</tr>
<tr>
<td>Resolution ≥50%</td>
<td>560 (77.1)</td>
<td>547 (77.3)</td>
</tr>
<tr>
<td><strong>Vascular death/MI, KM%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm</td>
<td>12.0 (7.5–18.0)</td>
<td>11.0 (7.0–17.5)</td>
</tr>
<tr>
<td>Discharge, mm</td>
<td>3.0 (1.0–5.0)</td>
<td>2.5 (1.0–5.0)</td>
</tr>
<tr>
<td>Resolution ≥50%</td>
<td>571 (78.7)</td>
<td>558 (78.8)</td>
</tr>
<tr>
<td><strong>1-y vascular death/MI, KM%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mm</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Vascular death, KM%</td>
<td>2.5</td>
<td>2.1</td>
</tr>
<tr>
<td>MI, KM%</td>
<td>4.0</td>
<td>4.6</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 χ² test; and in KM%, by the log-rank test. MI indicates myocardial infarction; ST-E, ST-elevation; ST-dev, ST-deviation; KM%, Kaplan-Meier estimates of event rates.

*P < 0.05 (between study treatments).
and MI within 1 year. Furthermore, no treatment effect of ticagrelor versus clopidogrel was evident on the resolution of the initial baseline ∑ST-dev at the conclusion of the 3-day interval between admission and hospital discharge. However, in comparison with clopidogrel, there was tendency for ticagrelor to provide greater benefit among those patients who achieved the greatest resolution of ∑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 ∑ST-dev resolution) are also those at increased risk of secondary vascular events, and hence amenable to more intense platelet inhibition therapy. To achieve this augmentation, for example, on reducing stent thrombosis without an increase in major bleeding is consistent with later benefit and less ischemia. Another mechanism of benefit could relate to inhibition of adenosine uptake by red blood cells favorably influencing myocardial perfusion. Finally, at least one-quarter of PLATO patients had impaired kidney function, a subpopulation in which clopidogrel is known to be of benefit. It is noteworthy that the magnitude of baseline ∑ST-E and ∑ST-dev we observed in the current investigation is considerably less than in previous studies involving both fibrinolytic and primary PCI; this probably reflects the later benefit and less ischemia. Another mechanism 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. Although we observed amplification of the benefit of ticagrelor in patients treated later after symptom onset and in those with greater ∑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 ∑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 ∑ST-dev resolution on prognosis is in accord with both fibrinolytic and primary PCI-treated patients from other studies in this laboratory.

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.

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Disclosures

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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 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 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 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, $p(\text{interaction})=0.368$), similar to that reported in Figure 2 of the corresponding manuscript. Similar observations were made regarding the resolution of $\Sigma$ST-dev (Figure A4, $p(\text{interaction})=0.815$).

SUPPLEMENTAL FIGURE 3.

![Graph showing HR vs Time from sx to rand, h for different values of $\Sigma$ST-D and resolution of $\Sigma$ST-dev.](image)

SUPPLEMENTAL FIGURE 4.

![Graph showing HR vs Time from sx to rand, h for different values of $\Sigma$ST-D resolution.](image)