Reduction in First and Recurrent Cardiovascular Events with Ticagrelor Compared with Clopidogrel in the PLATO Study

Running title: Kohli et al.; Ticagrelor and Recurrent Cardiovascular Events

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Abstract:

**Background**—We sought to evaluate the effect of potent platelet inhibition following acute coronary syndrome on total (i.e. first and recurrent) occurrences of any of the primary outcome events (e.g. cardiovascular death, myocardial infarction, and stroke) as well as on other ischemic events, such as urgent revascularization, (severe) recurrent ischemia (SRI/RI), transient ischemic attacks (TIA) and arterial thrombotic events (ATE).

**Methods and Results**—In the PLATelet inhibition and patient Outcomes (PLATO) study, 18,624 patients presenting with acute coronary syndromes randomly received ticagrelor (N=9333) or clopidogrel (N=9291). Cox proportional hazard models were used to calculate time to first event and hazard ratios. Total events were compared using a Poisson regression model and time to second event or death was calculated with the Wei Lin Weissfeld method. Patients randomized to ticagrelor had 1057 total primary endpoint events vs. 1225 for patients on clopidogrel (rate ratio=0.86, 95% CI 0.79-0.93, p=0.003). The number of additional events was numerically lower for ticagrelor (189 vs. 205, p=0.40), resulting in a hazard for time to second event/death of 0.80 (95% CI 0.70-0.90, p<0.001) and a number needed to treat of 54. For CVD/MI/Stroke/SRI/RI/TIA/ATE, total events were fewer with ticagrelor (2030 vs. 2290, rate ratio 0.88, 95% CI 0.82-0.95, p<0.001), with fewer recurrent events with ticagrelor (740 vs. 834, p=0.01) and a highly significant concurrent reduction in hazard for time to second event or death of 0.83 (95% CI 0.75-0.91, p<0.001). Recurrent PLATO major or TIMI major non-CABG bleeding events were infrequent and not different between the two therapies (p=0.96 and 0.38, respectively).

**Conclusions**—In PLATO, treatment with ticagrelor compared with clopidogrel resulted in a reduction in total events, including first and subsequent recurrent cardiovascular events, when compared to clopidogrel. These types of analyses demonstrate an even greater absolute benefit of ticagrelor over clopidogrel than previously reported.

**Clinical Trial Registration Information**—http://www.clinicaltrials.gov. Identifier: NCT00391872.

**Key words:** acute coronary syndrome; antiplatelet; antiplatelet therapy; clinical trials
Introduction

When analyzing the results of a large randomized controlled trial, patients are typically censored from endpoint analysis after the first occurrence of any component of the composite primary endpoints. This practice limits information to clinicians on the effect of the randomized therapy on subsequent events. Even though information is collected about subsequent (e.g., second, third, fourth, etc.) efficacy and safety endpoint events for the duration of trial follow-up, these data have not, in part by tradition, been included in the primary analysis. This leaves several unanswered questions for patients and physicians about the overall efficacy and risk of continued therapy in patients with an event while on study treatment.

Recently, several publications have demonstrated the clinical utility of conducting such “recurrent events” analyses, and analyzing the effect of the randomized treatment on not just the first occurrence of an endpoint, but on subsequent occurrences as well.1-4 Notably, in the Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38) study, platelet inhibition with the potent P2Y12 adenosine diphosphate (ADP) receptor inhibitor prasugrel reduced not only the first occurrence of the composite of death from cardiovascular causes, non-fatal myocardial infarction (MI), or non-fatal stroke, but also subsequent occurrences among those patients who survived their primary event.1

Therefore, we evaluated the effect of ticagrelor, a potent and reversibly binding P2Y12 ADP receptor antagonist, as compared with clopidogrel on recurrent cardiovascular events in PLATElet inhibition and patient Outcomes (PLATO). As previously reported, , ticagrelor reduced the rate of death from vascular causes (CVD), MI and stroke (HR 0.84, 95% CI 0.77-0.92, p<0.001), compared with less intensive platelet inhibition with clopidogrel.5 In this
analysis, we hypothesized that treatment with ticagrelor would reduce (1) the total number of primary events, including the first and subsequent occurrences of such events; and (2) the total number of ischemic events, tabulated by the first and subsequent occurrences of two additional pre-specified composite ischemic endpoints. We also investigated the effect of ticagrelor on recurrent bleeding events.

Methods

The results of the PLATO study have been previously published. Briefly, the study randomized 18,624 patients in a double-blind double-dummy fashion within 24 hours of an acute coronary syndrome (ACS) (either ST-elevation or non-ST-elevation) to ticagrelor (N=9333) or clopidogrel (N=9291). Ticagrelor was administered as a loading dose of 180 mg followed by 90 mg twice daily and clopidogrel was given as a 300-mg to 600 mg loading dose followed by 75 mg daily of maintenance therapy (for patients who had not been previously taking clopidogrel). All patients received background aspirin therapy at a daily dose of 75 to 100 mg. If PCI was performed, an additional dose of the study drug and 325 mg maintenance dose of aspirin were optionally permitted. Follow-up visits, with comprehensive review for adverse events and potential endpoints, were performed at 1, 3, 6, 9, and 12 months with another safety visit 1 month following completion of study treatment.

All endpoints, including recurrent endpoints, were pre-specified and adjudicated by an independent clinical events committee blinded to the randomization. CVD was defined as cardiovascular, cerebrovascular, or any death without another known cause. UR was defined as ischemia leading to revascularization within the same hospitalization or within 30 days of discharge. In this analysis, we also analyzed two pre-specified composite ischemic endpoints of
CVD/MI/stroke/severe recurrent ischemia/recurrent ischemia/transient ischemic attack/other arterial thrombotic events (CVD/MI/stroke/SRI/RI/TIA/ATE) and CVD/MI/stroke/UR, the individual components of which were collected and adjudicated during the trial.

All patients who experienced non-fatal events were recommended by protocol to remain on the randomized study drug but, independent of this choice, were included in the “recurrent” or “subsequent” events analysis. For example, if a patient had a non-fatal MI, this was counted towards the primary composite endpoint of CVD/MI/Stroke. If the same patient subsequently had a stroke, the stroke was counted towards the total number of events for that patient and, in addition, as a “recurrent” or “subsequent” event. Using this method, we weighted all events equally (i.e. death was weighted equally as recurrent ischemia). All analyses were conducted as intention to treat (ITT), except for safety/bleeding analyses, which were conducted as both intention to treat as well as on-treatment (i.e. a “safety” cohort). Drug discontinuation was defined as stopping drug within 7 days of (either before or after) a bleeding event.

Baseline characteristics for patients who experienced none, one, or multiple events are compared using a chi-square test for categorical variables and a Kruskall-Wallis test for continuous variables. Hazard ratios were computed using a Cox proportional hazards model. The proportional hazards assumption was assessed for each Cox model using the method of Lin, Wei, and Ying; the assumption was reasonable for all comparisons made. Total and mean number of events per patient (defined as total number of events divided by total number of patients randomized) were compared using a Poisson regression model. These results were reported as rate ratios (ratio of the mean number of events in each treatment group). In addition, number needed to treat (NNT) was calculated using total events. To verify that all differences were not driven entirely by the differences in first events, the analysis was repeated after excluding first
events. Also, time from randomization to second event (or death, including deaths that occurred as a first event) for the two treatment groups was compared with the Wei, Lin, Weissfeld method (WLW)\textsuperscript{7} to determine a hazard for ticagrelor vs. clopidogrel. All analyses were conducted with SAS, version 9.0 (SAS, Cary, North Carolina).

**Results**

Of the 1888 patients who experienced a primary endpoint event during follow-up for 6-12 months, 1570 developed only one event, but 318 patients experienced multiple occurrences of the composite endpoint of cardiovascular death/MI/stroke. **Table 1** shows a graded increase in the number of co-morbidities and cardiac risk factors observed among the respective patients with none, one and multiple events. Specifically, those with multiple events were more likely to be older or have diabetes mellitus, a prior history of MI or coronary artery bypass graft (CABG), impaired renal function and hypertension and less likely to be male. With respect to the index ACS event, patients with STEMI at study entry were more likely to experience no additional CVD/MI/stroke events during the trial whereas those with NSTEMI were more likely to experience multiple events (p<0.001).

**Efficacy**

As has been already reported, the first occurrence of the primary endpoint of the trial (CVD/MI/stroke) was reduced (HR 0.84, 95% CI 0.77-0.92, p<0.001) in patients on ticagrelor as compared with clopidogrel.\textsuperscript{6} In addition to the first occurrence, the hazard for the time to second occurrence of this composite endpoint or all-cause death was also significantly reduced by ticagrelor (HR 0.80, 95% CI 0.70-0.90, p<0.001). Accordingly, with respect to total number of events during the trial, ticagrelor resulted in fewer total CVD/MI/Stroke events as compared to
clopidogrel (1057 vs. 1225, NNT=54, Figure 1a), resulting in a favorable rate ratio of 0.86 (95% CI 0.79-0.93, p=0.003) (Table 2). Beyond the first event, there were numerically fewer additional events with ticagrelor (189 vs. 205, p=0.40), (Figure 1b) resulting in a lower calculated mean number of events per patient (Figure 1c), with divergence of curves occurring early.

Ticagrelor also effectively reduced the hazard for time to first of any atherothrombotic event (CVD/MI/Stroke/RI/SRI/TIA/ATE) to 0.88 (95% CI 0.82-0.95, p<0.001). Recurrent events (i.e., not including first events) were similarly reduced (740 vs. 834, p=0.01, Figure 2a), translating into a rate ratio of 0.88 (95% CI 0.83-0.94), with a highly significant concurrent reduction in hazard for time to second event or death of 0.83 (95% CI 0.75-0.91, p<0.001). There were fewer average endpoint events per patient of this ischemic endpoint with ticagrelor (Figure 2b), resulting in a NNT for this ischemic endpoint of 35, and fewer total events in this group (2030 vs. 2290, p<0.001, Figure 2a).

Concerning the other composite ischemic endpoint of CVD/MI/Stroke/UR, there were similar findings with superior efficacy of ticagrelor. Total events occurred less frequently with ticagrelor compared with clopidogrel (1325 vs. 1515, p<0.001, Figure 3a) resulting in a rate ratio of 0.87 (95% CI 0.81 vs. 0.94, p<0.001) and a NNT of 47. For this endpoint, there was a 14% decrease (95% CI 0.79-0.93, p<0.001) in the hazard ratio for time to first event and a 20% decrease (95% CI 0.71-0.91, p<0.001) in hazard for time to second event or death, and overall significantly fewer average number of events per patient (p<0.001) (Figure 3b). The findings were similar when data was analyzed on a “per-protocol” basis (Supplemental Table 1).

Safety

With respect to safety endpoints, potent platelet inhibition resulted in no difference in first,
second or total occurrences of PLATO major bleeding (which included CABG-related bleeding). In an on-treatment cohort, there were 961 first occurrences of PLATO major bleeding events with ticagrelor, compared with 929 with clopidogrel (HR 1.04, p=0.43; Figure 4a). Furthermore, recurrent bleeding events tended to be infrequent compared to the first occurrences in both ticagrelor and clopidogrel arms (70 vs. 68, rate ratio 1.02, p=0.89). This resulted in a similar number of total PLATO major bleeding events with ticagrelor and clopidogrel (1031 and 997, rate ratio 1.03, p=0.53, Figure 4a) and, accordingly, similar numbers of average bleeding events per patient (Figure 4b). When analyzing safety results in an “ITT” cohort, counting all bleeds, on or off study drug, the rates of bleeding were similar between the two treatments (1224 vs. 1208 for ticagrelor and clopidogrel), with rate ratio 1.01, p=0.83 for total events; and 106 vs. 113, with a rate ratio 0.93, p=0.61 for additional events.

Although there was no difference between ticagrelor and clopidogrel in major bleeding, there were some differences in minor bleeding. Ticagrelor increased the total number of PLATO major or minor events in the on-treatment population (rate ratio=1.09, 95% CI 1.01-1.17, p=0.02) and the ITT population (rate ratio=1.08, 95% CI 1.01-1.16, p=0.03). This was driven primarily by the first occurrences of this composite bleeding endpoint, with no difference in additional bleeding events in either the ITT cohort (228 vs. 226 events, rate ratio=1.00, p=0.96) or the on-treatment cohort (168 vs. 162 events, rate ratio=1.03, p=0.78).

Analyzing TIMI major non-CABG bleeding endpoints, in the on-treatment cohort, there were statistically more total bleeding events (234 vs. 188, rate ratio 1.24, p=0.03) as well as a greater mean number of bleeds per patient in the ticagrelor group. These appear to have been driven primarily by the first occurrence of this endpoint (221 vs. 177, p=0.03). When analyzed in an ITT fashion including those who prematurely discontinued study drug, results were
qualitatively similar for TIMI major non-CABG bleeding (265 vs. 227 events, p=0.10).

However, although first occurrences of bleeding increased with ticagrelor, recurrent bleeding events were uncommon and similar by treatment for both the safety cohort (13 vs. 11, p=0.69) as well as the ITT cohort (18 vs. 13, p=0.38).

After a bleeding event, there was no difference between treatment groups in the number of patients who discontinued randomized therapy as a result of the bleed. After a PLATO major bleeding event, there were 8.1% patients who discontinued ticagrelor, and 8.9% who discontinued clopidogrel. Similarly, after experiencing PLATO major or minor bleeding, the rates of drug discontinuation were identical in both arms (10.8%). Following a TIMI major non-CABG related bleeding event 34.3% and 31.4% of patients discontinued clopidogrel and ticagrelor (respectively).

Discussion

This analysis from PLATO demonstrates that in patients with ACS, treatment with ticagrelor, a potent reversibly-binding P2Y12-inhibitor, compared with the less potent irreversible agent clopidogrel, resulted in a greater prevention of not only first, but also subsequent, occurrences of cardiovascular events. We found that ticagrelor resulted in continuously lower event rates than clopidogrel and thus fewer total ischemic events as compared with clopidogrel. Furthermore, in the two thirds of patients who continued treatment with ticagrelor or clopidogrel after an initial bleed, ticagrelor was not associated with any further increase in recurrent bleeding events, including PLATO major bleeding or TIMI major non-CABG bleeding events. Therefore, when taking all events into account, the benefit of using ticagrelor in patients with ACS is even larger than previously reported with the protocol-based analyses focusing only on the first event.5
In clinical trials, it is a common practice to censor patient outcome data after the first occurrence of any component of a composite endpoint has occurred, even though information is collected for the duration of follow-up about all events. Although this provides important information about the first event, many unanswered questions remain about subsequent events. In clinical practice, it is unclear whether the intervention of interest should be continued if someone experiences an event while on therapy. Precedent from cost-effectiveness analyses has demonstrated the utility of including not only the first event, but also the second, third, and all subsequent events in the analysis.8-10

Such recurrent events analyses previously conducted with other potent P2Y12 platelet inhibitors in ACS, such as in TRITON-TIMI 38, have established precedent and demonstrated the efficacy of ongoing potent platelet inhibition resulting in improvement in outcomes.1 Previously, ticagrelor has been reported to reduce first occurrence of CVD/MI/Stroke by 16%.5 In the present study, we demonstrated the superiority of ongoing treatment with ticagrelor in decreasing total occurrences of this endpoint, as well as two additional pre-specified composite ischemic endpoints. Based on these total event analyses, we report a NNT of 54 to prevent one occurrence of CVD/MI/Stroke and even lower numbers (NNT=35 and NNT=47) for the reduction of the other expanded ischemic endpoints. This effect of acute and long-term treatment with ticagrelor compared to clopidogrel is rather similar to the NNT for other established effective interventions, such as intensive statin therapy (NNT=59 for coronary heart death/MI with atorvastatin 80 mg vs. pravastatin 40 mg).11

Although the efficacy of potent platelet inhibition was sustained, recurrent bleeding with continued therapy was very infrequent following the first occurrence of this event (with a similar rates of drug discontinuation in each arm, in about 1/3 of patients): there were only 70 vs. 68
incidents of recurrent PLATO major bleeding events throughout the follow-up period. With either definition of bleeding (PLATO or TIMI major non-CABG), only 5-7% of patients who had one bleed would go on to develop a recurrent bleed, even in the cohorts who stayed on study drug. This illustrates that the lack of a difference in recurrent bleeding events could not be attributed to a higher rate of discontinuation. This also suggests that the bleeding risk for potent P2Y12 inhibitors is highest initially, and wanes after the first bleeding event. Therefore, once a patient has a bleeding event, he/she appears to be relatively unlikely to have a recurrent bleed.

However, the benefit in preventing ischemic events of continuing treatment with ticagrelor as compared to clopidogrel is maintained. Our results were similar when analyzed either as an intention-to-treat analysis or an on-treatment analysis. These results are consistent with previously reported effects of more intensive platelet inhibition with prasugrel vs. clopidogrel,1,12 and of intensive statin therapy vs. standard statin,2-4 where the more intensive therapy reduced both first and recurrent events.

Limitations

Although our analysis provides valuable information, there are limitations to studying recurrent events. Although the WLW survival analysis for recurrent events has been a well-validated model with respect to studying recurrent events,7 there are assumptions inherent to this model, such as independence among first and recurrent events, which may not be valid. Furthermore, in such an analysis, survival bias may influence results (i.e. those who live longer are more likely to have recurrent events) although any such effect would tend to diminish the efficacy differences between ticagrelor and clopidogrel and therefore, appears unlikely in view of improved survival with the former. For those endpoints such as CVD/MI/Stroke, where recurrent events are relatively infrequent compared with more comprehensive composite ischemic endpoints, the
comparison of only the additional events will be limited by low statistical power. For these reasons, we focused our comparisons on the total events analysis with its higher power, and maintenance of randomization. Thus, by counting total events and mean number of events by randomization arm, we maintain the integrity of the randomization and therefore avoid the assumption, confounding and bias that may be inherent in other analyses of total and recurrent events. Finally, for the bleeding analyses, 1/3 of patients discontinued (in each arm) study treatment following a bleed, limiting somewhat the comparisons of recurrent bleeding rates.

Conclusion

Treatment with ticagrelor, as compared with clopidogrel, not only reduces the first occurrence but also repeated cardiovascular events and thereby reduces total number of cardiovascular events. This results in a low overall NNT. Ticagrelor treatment is associated with a slightly increased risk of having a first non-CABG major bleed but, thereafter, the bleeding risk is similar to clopidogrel despite continuing unchanged long-term treatment. Clinically, these results have important implications for guiding physicians to continue ticagrelor therapy, rather than changing therapy to alternative agents, even for patients who may experience an event while on treatment.

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Conflict of Interest Disclosures: Dr. Kohli reports honoraria from serving on an advisory board for Daiichi-Sankyo. Dr. Wallentin reports research grants from AstraZeneca, Merck/Schering-Plough, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline; being a consultant for Merck/Schering-Plough, Regado Biosciences, Evolva, Protola, C.S.L. Behring, Athera Biotechnologies, Boehringer-Ingelheim, AstraZeneca, GlaxoSmithKline, and Bristol-Myers Squibb/Pfizer; he also reports lecture fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Schering-Plough, and honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and
Schering-Plough/Merck. Dr Horrow is an employee of AstraZeneca and has equity ownership in AstraZeneca. Dr. Husted reports receiving advisory board fees from AstraZeneca, Bristol-Myers Squibb, and Bayer. Dr. Angiolillo has received honoraria for lectures from Bristol Myers Squibb; Sanofi-Aventis; Eli Lilly Co; Daiichi Sankyo, Inc; Astra Zeneca, and consulting fees from Bristol Myers Squibb; Sanofi-Aventis; Eli Lilly Co; Daiichi Sankyo, Inc.; The Medicines Company; Portola; Novartis; Medicure; Accumetrics; Arena Pharmaceuticals; Astra Zeneca; Merck; Evolva; Abbott Vascular; research grants paid to Institution from Bristol Myers Squibb; Sanofi-Aventis; GlaxoSmithKline; Otsuka; Eli Lilly Co; Daiichi Sankyo, Inc., The Medicines Company; Portola; Accumetrics; Schering-Plough; Astra-Zeneca; Eisai; CSL Parexel. Dr. Maurer reports receiving advisory board fees from AstraZeneca, Merck, Boehringer-Ingelheim, Roche, and Bayer. Dr. Morais has received payments from speakers’ bureau from AstraZeneca, Bayer, and MSD; honoraria from AstraZeneca, Bayer, JABA Recordati, and MSD. Dr. Nicolau reports having research grants and receiving honoraria from AstraZeneca, Eli-Lilly/Daiichi Sankyo, Sanofi, MSD and Bayer. Dr. Oto reports receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Servier, and serving as an advisory board member for MSD. Dr Storey reports having research grants from AstraZeneca, Eli Lilly/Daiichi Sankyo, and Merck, receiving research support from Accumetrics and honoraria from AstraZeneca, Eli Lilly/Daiichi Sankyo, Merck, Novartis, The Medicines Company, Iroko, Sanofi-Aventis/BMS, GlaxoSmithKline, Accumetrics, Medscape, and Eisai; he also reports receiving consultancy fees from AstraZeneca, Merck, Novartis, Accumetrics, and Eisai. Dr. James reports having institutional research grant and receiving honoraria from AstraZeneca, Eli Lilly, Merck and Bristol-Myers Squibb and being an advisory board member for AstraZeneca, Eli Lilly and Merck. He also has received honoraria from The Medicines Company. Dr. Cannon reports having research grants/support: Accumetrics, AstraZeneca, Essentialis, GlaxoSmithKline, Merck, Regeneron, Sanofi, Takeda. He also has served on advisory boards for Alnylam, Bristol-Myers Squibb, CSL Behring, Pfizer, but all funds are donated to charity. He is a clinical Advisor, and holds equity in Automedics Medical Systems.

References:


**Table 1.** Baseline Characteristics of patients with No Events, a Single Event, or Multiple CVD/MI/Stroke Events

<table>
<thead>
<tr>
<th></th>
<th>None (n=16,736)</th>
<th>Single (n=1,570)</th>
<th>Multiple (n=318)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – year ± SD</strong></td>
<td>62 ± 11</td>
<td>66 ± 11</td>
<td>67 ± 11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Male sex – no. (%)</strong></td>
<td>12,055 (72.0)</td>
<td>1,080 (68.8)</td>
<td>201 (63.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Weight – kg ± SD</strong></td>
<td>81 ± 16</td>
<td>78 ± 16</td>
<td>76 ± 16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>92.1</td>
<td>89.3</td>
<td>84.9</td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>1.2</td>
<td>1.8</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Oriental (%)</td>
<td>5.7</td>
<td>7.1</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>1.1</td>
<td>1.8</td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension – no. (%)</strong></td>
<td>10,788 (64.5)</td>
<td>1,145 (72.9)</td>
<td>250 (78.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Dyslipidemia – no. (%)</strong></td>
<td>7,742 (46.3)</td>
<td>786 (50.1)</td>
<td>161 (50.6)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus – no. (%)</strong></td>
<td>4,000 (23.9)</td>
<td>539 (34.3)</td>
<td>123 (38.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Current/Previous Smoking – no. (%)</strong></td>
<td>10,282 (61.5)</td>
<td>892 (56.8)</td>
<td>180 (56.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prior MI – no. (%)</strong></td>
<td>3,253 (19.4)</td>
<td>446 (28.4)</td>
<td>125 (39.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Prior CABG – no. (%)</strong></td>
<td>893 (5.3)</td>
<td>169 (10.8)</td>
<td>44 (13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CrCl &lt;60 ml/min – no. (%)</strong></td>
<td>2,644 (15.8)</td>
<td>482 (30.7)</td>
<td>111 (34.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Index ACS: STEMI – no. (%)</strong></td>
<td>6,402b(38.3)</td>
<td>527 (33.7)</td>
<td>97 (30.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Index ACS: NSTEMI – no. (%)</strong></td>
<td>7,009 (42.0)</td>
<td>778 (49.8)</td>
<td>168 (53.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Troponin + at entry – no. (%)</strong></td>
<td>13,472 (80.5)</td>
<td>1,340 (85.4)</td>
<td>277 (87.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Randomized to Ticagrelor – no. (%)</strong></td>
<td>8,456 (50.6)</td>
<td>714 (45.5)</td>
<td>154 (48.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p-value from chi-square test (categorical variables) or Kruskall-Wallis test (continuous variables) across the three categories.*
Table 2. Time from randomization to 1st event, time from randomization to 2nd event or death, the total number of events, depicted as hazard ratios or risk ratios (95% CIs) and the number needed to treat to prevent one event.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time to 1st Event</th>
<th>Time to 2nd Event or Death</th>
<th>Total # of Events</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, MI, Stroke</td>
<td>HR 0.84 (0.77-0.92)</td>
<td>HR 0.80 (0.70-0.90)</td>
<td>RR 0.86 (0.79-0.93)</td>
<td>54</td>
</tr>
<tr>
<td>CV Death, MI, Stroke, SRI, RI, TIA, ATE</td>
<td>HR 0.88 (0.82-0.95)</td>
<td>HR 0.83 (0.75-0.91)</td>
<td>RR 0.88 (0.83-0.94)</td>
<td>35</td>
</tr>
<tr>
<td>CV Death, MI, Stroke, Urgent Revascularization</td>
<td>HR 0.86 (0.79-0.93)</td>
<td>HR 0.80 (0.71-0.91)</td>
<td>RR 0.87 (0.81-0.94)</td>
<td>47</td>
</tr>
</tbody>
</table>


Figure Legends:

Figure 1. (a) First, additional and total events for the composite endpoints of CVD/MI/stroke demonstrated fewer first and total events with ticagrelor; (b) Number of first and subsequent events (by the specific type of event) for the components of the primary endpoint; No formal comparisons are made.* As described in the Methods, one cannot simply compare the number of second events – one needs to either compare the total number of events (that preserves the balance of randomization and counts all patients), or use models like the WLW analysis reported in the main paper to account for the first event. (c) Mean number of occurrences of CVD/MI/stroke per patient was decreased with ticagrelor for the duration of the follow-up.

Abbreviations used: CVD: cardiovascular death, MI: myocardial infarction.
Figure 2. (a) First, additional and total events for the composite endpoint of CVD/MI/Stroke/SRI/RI/TIA/ATE show fewer events with ticagrelor; (b) Mean number of CVD/MI/Stroke/SRI/RI/TIA/ATE events per patient was lower during the trial in the ticagrelor arm compared with clopidogrel. Abbreviations used: CVD: cardiovascular death, MI: myocardial infarction, SRI: severe recurrent ischemia, RI: recurrent ischemia, TIA: transient ischemic attack, ATE: arterial thrombosis.

Figure 3. (a) First, additional and total events for the composite endpoints of CVD/MI/Stroke/UR demonstrated fewer first and total events with ticagrelor; (b) Mean number of CVD/MI/Stroke/UR events per patient was lower during the trial in the ticagrelor arm compared with clopidogrel. Abbreviations used: CVD: cardiovascular death, MI: myocardial infarction, UR: Urgent Revascularization.

Figure 4. (a) First, additional and total and (b) mean number of PLATO major bleeding events.
Figure 1a

- Ticagrelor:
  - Total Events: 868
  - First Events: 189
  - Additional Events: 205
  - P = 0.003
  - P = 0.40

- Clopidogrel:
  - Total Events: 1020
  - First Events: 1020
  - P = 0.002

n = 1225
Figure 1b

First Event

- Clopidogrel
- Ticagrelor

Subsequent Events

- Clopidogrel
- Ticagrelor

Legend:
- CV Death
- MI
- Stroke
Mean Events: CVD / MI / Stroke

- Total n = 1057
- Total n = 1225
- p=0.003
- NNT=54

Figure 1c
NNT=35

Total n = 2030

Total n = 2290

p<0.001

Figure 2b
Figure 3a

Number of events

Ticagrelor

- Total Events: 1325
- Additional Events: 255
- First Events: 1070
- P-value: <0.001

Clopidogrel

- Total Events: 1515
- Additional Events: 279
- First Events: 1236
- P-value: 0.28

P = 0.28
Figure 3b

Total n = 1325

Total n = 1515

NNT = 47

p < 0.001
Figure 4b
Reduction in First and Recurrent Cardiovascular Events with Ticagrelor Compared with Clopidogrel in the PLATO Study
Payal Kohli, Lars Wallentin, Eric Reyes, Jay Horrow, Steen Husted, Dominick J. Angiolillo, Diego Ardissino, Gerald Maurer, Joao Morais, José C. Nicolau, Ali Oto, Robert F. Storey, Stefan K. James and Christopher P. Cannon

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL Table 1 .

A “per-protocol” analysis of time from randomization to 1st event, time from randomization to 2nd event or death, the total number of events, depicted as hazard ratios or risk ratios (95% CIs)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time* to 1st Event</th>
<th>Time* to 2nd Event</th>
<th>Total Number of Events</th>
<th>Secondary Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death, MI, Stroke</td>
<td>0.84 (0.77, 0.92)</td>
<td>0.79 (0.70, 0.88)</td>
<td>0.86 (0.79, 0.93)</td>
<td>0.92 (0.75, 1.12)</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.395</td>
</tr>
<tr>
<td>CV Death, MI, Stroke, SRI, RI, TIA, ATE</td>
<td>0.88 (0.81, 0.95)</td>
<td>0.83 (0.76, 0.91)</td>
<td>0.88 (0.83, 0.94)</td>
<td>0.88 (0.80, 0.98)</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.014</td>
</tr>
<tr>
<td>CV Death, MI, Stroke, Urgent Revasc</td>
<td>0.86 (0.79, 0.93)</td>
<td>0.80 (0.71, 0.89)</td>
<td>0.87 (0.81, 0.94)</td>
<td>0.91 (0.77, 1.08)</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p = 0.276</td>
</tr>
</tbody>
</table>