Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

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Abstract

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*The Study of Platelet Inhibition and Patient Outcomes (PLATO) investigators are listed in the Appendix and the Supplementary Appendix, available with the full text of this article at NEJM.org.

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In patients who have acute coronary syndromes with or without ST-segment elevation, current clinical practice guidelines recommend dual antiplatelet treatment with aspirin and clopidogrel. The efficacy of clopidogrel is hampered by the slow and variable transformation of the prodrug to the active metabolite, modest and variable platelet inhibition, an increased risk of bleeding, and an increased risk of stent thrombosis and myocardial infarction in patients with a poor response. As compared with clopidogrel, prasugrel, another thienopyridine prodrug, has a more consistent and pronounced inhibitory effect on platelets resulting in a lower risk of myocardial infarction and stent thrombosis, but is associated with a higher risk of major bleeding in patients with an acute coronary syndrome who are undergoing percutaneous coronary intervention (PCI).

Ticagrelor, a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor P2Y12, provides faster, greater, and more consistent P2Y12 inhibition than clopidogrel. In a dose-guiding trial, there was no significant difference in the rate of bleeding with the use of ticagrelor at a dose of 90 mg or 180 mg twice daily and the rate with the use of clopidogrel at a dose of 75 mg daily. However, dose-related episodes of dyspnea and ventricular pauses on Holter monitoring, which occurred more frequently with ticagrelor, led to the selection of the dose of 90 mg twice daily for further studies. We conducted the Study of Platelet Inhibition and Patient Outcomes (PLATO) to determine whether ticagrelor is superior to clopidogrel for the prevention of vascular events and death in a broad population of patients presenting with an acute coronary syndrome.

**METHODS**

**STUDY DESIGN**

PLATO was a multicenter, randomized, double-blind trial. The details of the design have been published previously. The executive and operations committee, consisting of both academic members and representatives of the sponsor, AstraZeneca, designed and oversaw the conduct of the trial. An independent data and safety monitoring board monitored the trial and had access to the unblinded data. The sponsor coordinated the data management. Statistical analysis was performed by Worldwide Clinical Trials, a contract research organization, in collaboration with investigators at the academic centers and the sponsor, all of whom had full access to the final study data. The manuscript was drafted by the chairs of the executive and operations committee, who were academic authors and who vouch for the accuracy and completeness of the reported data. The study design was approved by the appropriate national and institutional regulatory authorities and ethics committees, and all participants provided written informed consent.

**STUDY PATIENTS**

Patients were eligible for enrollment if they were hospitalized for an acute coronary syndrome, with or without ST-segment elevation, with an onset of symptoms during the previous 24 hours. For patients who had an acute coronary syndrome without ST-segment elevation, at least two of the following three criteria had to be met: ST-segment changes on electrocardiography, indicating ischemia; a positive test of a biomarker, indicating myocardial necrosis; or one of several risk factors (age ≥60 years; previous myocardial infarction or coronary-artery bypass grafting [CABG]; coronary artery disease with stenosis of ≥50% in at least two vessels; previous ischemic stroke, transient ischemic attack, carotid stenosis of at least 50%, or cerebral revascularization; diabetes mellitus; peripheral arterial disease; or chronic renal dysfunction, defined as a creatinine clearance of <60 ml per minute per 1.73 m² of body-surface area). For patients who had an acute coronary syndrome with ST-segment elevation, the following two inclusion criteria had to be met: persistent ST-segment elevation of at least 0.1 mV in at least two contiguous leads or a new left bundle-branch block, and the intention to perform primary PCI. Major exclusion criteria were any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 hours before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer.

**STUDY TREATMENT**

Patients were randomly assigned to receive ticagrelor or clopidogrel, administered in a double-blind, double-dummy fashion. Ticagrelor was given in a loading dose of 180 mg followed by a dose of 90 mg twice daily. Patients in the clopidogrel group who had not received an open-label...
loading dose and had not been taking clopidogrel for at least 5 days before randomization received a 300-mg loading dose followed by a dose of 75 mg daily. Others in the clopidogrel group continued to receive a maintenance dose of 75 mg daily. Patients undergoing PCI after randomization received, in a blind fashion, an additional dose of their study drug at the time of PCI: 300 mg of clopidogrel, at the investigator's discretion, or 90 mg of ticagrelor for patients who were undergoing PCI more than 24 hours after randomization. In patients undergoing CABG, it was recommended that the study drug be withheld — in the clopidogrel group, for 5 days, and in the ticagrelor group, for 24 to 72 hours. All patients received acetylsalicylic acid (aspirin) at a dose of 75 to 100 mg daily unless they could not tolerate the drug. For those who had not previously been receiving aspirin, 325 mg was the preferred loading dose; 325 mg was also permitted as the daily dose for 6 months after stent placement.

Outpatient visits were scheduled at 1, 3, 6, 9, and 12 months, with a safety follow-up visit 1 month after the end of treatment. The randomized treatment was scheduled to continue for 12 months, but patients left the study at their 6- or 9-month visit if the targeted number of 1780 primary end-point events had occurred by that time. Initially, patients were to be assessed by means of Holter monitoring for 7 days after randomization, until a repeat assessment at 1 month had been obtained for 2000 of the enrolled patients.

END POINTS

Death from vascular causes was defined as death from cardiovascular causes or cerebrovascular causes and any death without another known cause. Myocardial infarction was defined in accordance with the universal definition proposed in 2007.14,15 Evaluation for stent thrombosis was performed according to the Academic Research Consortium criteria.16 Stroke was defined as focal loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 hours or leading to death.

We defined major life-threatening bleeding as fatal bleeding, intracranial bleeding, intrapericardial bleeding with cardiac tamponade, hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery, a decline in the hemoglobin level of 5.0 g per deciliter or more, or the need for transfusion of at least 4 units of red cells. We defined other major bleeding as bleeding that led to clinically significant disability (e.g., intraocular bleeding with permanent vision loss) or bleeding either associated with a drop in the hemoglobin level of at least 3.0 g per deciliter but less than 5.0 g per deciliter or requiring transfusion of 2 to 3 units of red cells. We defined minor bleeding as any bleeding requiring medical intervention but not meeting the criteria for major bleeding.

An independent central adjudication committee adjudicated all suspected primary and secondary efficacy end points as well as major and minor bleeding events.

STATISTICAL ANALYSIS

The primary efficacy variable was the time to the first occurrence of composite of death from vascular causes, myocardial infarction, or stroke. We estimated that 1780 such events would be required to achieve 90% power to detect a relative risk reduction of 13.5% in the rate of the primary end point in the ticagrelor group as compared with the clopidogrel group, given an event rate of 11% in the clopidogrel group at 12 months. Cox proportional-hazards models were used to analyze the data on primary and secondary end points. All patients who had been randomly assigned to a treatment group were included in the intention-to-treat analyses.

The principal secondary efficacy end point was the primary efficacy variable studied in the subgroup of patients for whom invasive management was planned at randomization. Additional secondary end points (analyzed for the entire study population) were the composite of death from any cause, myocardial infarction, or stroke; the composite of death from vascular causes, myocardial infarction, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, transient ischemic attack, or other arterial thrombotic events; myocardial infarction alone; death from cardiovascular causes alone; stroke alone; and death from any cause.

To address the issue of multiple testing, a hierarchical test sequence was planned. The secondary composite efficacy end points were tested individually, in the order in which they are listed above, until the first nonsignificant difference was found between the two treatment groups. Other treatment comparisons were examined in an exploratory manner. No multiplicity adjustment was made to the confidence intervals for...
Table 1. Baseline Characteristics of the Patients, According to Treatment Group.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ticagrelor Group</th>
<th>Clopidogrel Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age — yr</td>
<td>62.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Age ≥75 yr — no./total no. (%)</td>
<td>1396/9333 (15.0)</td>
<td>1482/9291 (16.0)</td>
</tr>
<tr>
<td>Female sex — no./total no. (%)</td>
<td>2655/9333 (28.4)</td>
<td>2633/9291 (28.3)</td>
</tr>
<tr>
<td>Median body weight — kg (range)</td>
<td>80.0 (28–174)</td>
<td>80.0 (29–180)</td>
</tr>
<tr>
<td>Body weight &lt;60 kg — no./total no. (%)</td>
<td>652/9333 (7.0)</td>
<td>660/9291 (7.1)</td>
</tr>
<tr>
<td>BMI — median (range)†</td>
<td>27 (13–68)</td>
<td>27 (13–70)</td>
</tr>
<tr>
<td>Race — no./total no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8566/9332 (91.8)</td>
<td>8511/9291 (91.6)</td>
</tr>
<tr>
<td>Black</td>
<td>115/9332 (1.2)</td>
<td>114/9291 (1.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>542/9332 (5.8)</td>
<td>554/9291 (6.0)</td>
</tr>
<tr>
<td>Other</td>
<td>109/9332 (1.2)</td>
<td>112/9291 (1.2)</td>
</tr>
<tr>
<td>Cardiovascular risk factor — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Habitual smoker</td>
<td>3360/9333 (36.0)</td>
<td>3318/9291 (35.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6139/9333 (65.8)</td>
<td>6044/9291 (65.1)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4347/9333 (46.6)</td>
<td>4342/9291 (46.7)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>2326/9333 (24.9)</td>
<td>2336/9291 (25.1)</td>
</tr>
<tr>
<td>Other medical history — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>1900/9333 (20.4)</td>
<td>1924/9291 (20.7)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>1272/9333 (13.6)</td>
<td>1220/9291 (13.1)</td>
</tr>
<tr>
<td>Coronary-artery bypass grafting</td>
<td>532/9333 (5.7)</td>
<td>574/9291 (6.2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>513/9333 (5.5)</td>
<td>537/9291 (5.8)</td>
</tr>
<tr>
<td>Nonhemorrhagic stroke</td>
<td>353/9333 (3.8)</td>
<td>369/9291 (4.0)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>566/9333 (6.1)</td>
<td>578/9291 (6.2)</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>379/9333 (4.1)</td>
<td>406/9291 (4.4)</td>
</tr>
<tr>
<td>History of dyspnea</td>
<td>1412/9333 (15.1)</td>
<td>1358/9291 (14.6)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>555/9333 (5.9)</td>
<td>530/9291 (5.7)</td>
</tr>
<tr>
<td>Asthma</td>
<td>267/9333 (2.9)</td>
<td>265/9291 (2.9)</td>
</tr>
<tr>
<td>Gout</td>
<td>272/9333 (2.9)</td>
<td>262/9291 (2.8)</td>
</tr>
<tr>
<td>ECG findings at study entry — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent ST-segment elevation</td>
<td>3497/9333 (37.5)</td>
<td>3511/9291 (37.8)</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>4730/9333 (50.7)</td>
<td>4756/9291 (51.2)</td>
</tr>
<tr>
<td>T-wave inversion</td>
<td>2970/9333 (31.8)</td>
<td>2975/9291 (32.0)</td>
</tr>
<tr>
<td>Positive troponin I test at study entry — no./total no. (%)</td>
<td>7965/9333 (85.3)</td>
<td>7999/9291 (86.1)</td>
</tr>
<tr>
<td>Final diagnosis of ACS — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST-elevation MI</td>
<td>3496/9333 (37.5)</td>
<td>3530/9291 (38.0)</td>
</tr>
<tr>
<td>Non–ST-elevation MI</td>
<td>4005/9333 (42.9)</td>
<td>3950/9291 (42.5)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1549/9333 (16.6)</td>
<td>1563/9291 (16.8)</td>
</tr>
<tr>
<td>Other diagnosis or missing data§</td>
<td>283/9333 (3.0)</td>
<td>248/9291 (2.7)</td>
</tr>
<tr>
<td>Risk factors for ST-elevation MI — no./total no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Killip class &gt;2</td>
<td>25/3496 (0.7)</td>
<td>41/3530 (1.2)</td>
</tr>
<tr>
<td>TIMI risk score ≥3</td>
<td>1584/3496 (45.3)</td>
<td>1553/3530 (44.0)</td>
</tr>
</tbody>
</table>
the hazard ratios for the ticagrelor group as compared with the clopidogrel group.

The consistency of treatment effects over time was assessed by determining the relative risk ratios for the periods from randomization to 30 days and from 31 to 360 days. Another predefined objective was to compare the two treatment groups with respect to the occurrence of stent thrombosis. The primary safety end point was the first occurrence of any major bleeding event. Additional safety end points included minor bleeding, dyspnea, bradyarrhythmia, any other clinical adverse event, and results of laboratory safety tests. The consistency of effects on efficacy and safety end points was explored in 25 prespecified subgroups and 8 post hoc subgroups, without adjustment for multiple comparisons.

**Results**

**Study Patients and Study Drugs**

We recruited 18,624 patients from 862 centers in 43 countries from October 2006 through July 2008. The follow-up period ended in February 2009, when information on vital status was available for all patients except five. The two treatment groups were well balanced with regard to all baseline characteristics (Table 1) and non-study medications and procedures (Table 2). Both groups started the study drug at a median of 11.3 hours (interquartile range, 4.8 to 19.8) after the start of chest pain. In the clopidogrel group, taking into account both open-label and randomized treatment, 79.1% of patients received at least 300 mg, and 19.6% at least 600 mg, of clopidogrel between the time of the index event and up to 24 hours after randomization. Premature discontinuation of the study drug was slightly more common in the ticagrelor group than in the clopidogrel group (in 23.4% of patients vs. 21.5%). The overall rate of adherence to the study drug, as assessed by the site investigators, was 82.8%, and the median duration of exposure to the study drug was 277 days (interquartile range, 179 to 365).

**Efficacy**

The primary end point occurred significantly less often in the ticagrelor group than in the clopidogrel group (in 9.8% of patients vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001) (Table 3 and Fig. 1). The difference in treatment effect was apparent within the first 30 days of therapy and persisted throughout the study period. As shown in Table 3 (and Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), the hierarchical testing of secondary end points showed significant reductions in the ticagrelor group, as compared with the clopidogrel group, with respect to the rates of the composite end point of death from any cause, myocardial infarction, or stroke (10.2% vs. 12.3%, P<0.001); the composite end point of death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, recurrent ischemia, transient ischemic attack, or other arterial throm-
Table 2. Randomized Treatment, Other Treatments, and Procedures, According to Treatment Group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ticagrelor Group (N = 9333)</th>
<th>Clopidogrel Group (N = 9291)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of randomized treatment</td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>Patients receiving treatment — no. (%)</td>
<td>9235 (98.9)</td>
<td>9186 (98.9)</td>
<td></td>
</tr>
<tr>
<td>Time after start of chest pain — hr</td>
<td>11.3</td>
<td>11.3</td>
<td>0.75</td>
</tr>
<tr>
<td>Median</td>
<td>4.8–19.8</td>
<td>4.8–19.8</td>
<td></td>
</tr>
<tr>
<td>Time after start of hospitalization — hr</td>
<td>4.9</td>
<td>5.3</td>
<td>0.11</td>
</tr>
<tr>
<td>Median</td>
<td>1.3–18.8</td>
<td>1.4–15.8</td>
<td></td>
</tr>
<tr>
<td>Premature discontinuation of study drug — no. (%)</td>
<td>2186 (23.4)</td>
<td>1999 (21.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Because of adverse event</td>
<td>690 (7.4)</td>
<td>556 (6.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Because of patient’s unwillingness to continue</td>
<td>946 (10.1)</td>
<td>859 (9.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Other reason</td>
<td>550 (5.9)</td>
<td>584 (6.3)</td>
<td>0.27</td>
</tr>
<tr>
<td>Adherence to study drug — no. (%)</td>
<td>7724 (82.8)</td>
<td>7697 (82.8)</td>
<td>0.89</td>
</tr>
<tr>
<td>Exposure to study drug — days</td>
<td>277</td>
<td>277</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel administered in hospital before randomization — no. (%)</td>
<td>4293 (46.0)</td>
<td>4282 (46.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Clopidogrel dose given (as study drug or not) within 24 hours before or after randomization — no. (%)</td>
<td>4937 (52.9)</td>
<td>94 (1.0)</td>
<td>0.65</td>
</tr>
<tr>
<td>No loading dose, or missing information</td>
<td>1921 (20.6)</td>
<td>5528 (59.5)</td>
<td></td>
</tr>
<tr>
<td>300–375 mg</td>
<td>1282 (13.7)</td>
<td>1822 (19.6)</td>
<td></td>
</tr>
<tr>
<td>600–675 mg</td>
<td>697 (7.5)</td>
<td>1339 (14.4)</td>
<td></td>
</tr>
<tr>
<td>Other dose</td>
<td>251 (2.7)</td>
<td>246 (2.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Same dose as that given before index event</td>
<td>496 (5.3)</td>
<td>508 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Antithrombotic treatment in hospital — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before randomization</td>
<td>8827 (94.6)</td>
<td>8755 (94.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>After randomization</td>
<td>9092 (97.4)</td>
<td>9056 (97.5)</td>
<td>0.85</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>5304 (56.8)</td>
<td>5233 (56.3)</td>
<td>0.49</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>4813 (51.6)</td>
<td>4706 (50.7)</td>
<td>0.21</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>251 (2.7)</td>
<td>246 (2.6)</td>
<td>0.89</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>188 (2.0)</td>
<td>183 (2.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>2468 (26.4)</td>
<td>2487 (26.8)</td>
<td>0.62</td>
</tr>
<tr>
<td>Other medication administered in hospital or at discharge — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organic nitrate</td>
<td>7181 (76.9)</td>
<td>7088 (76.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>8339 (89.3)</td>
<td>8336 (89.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>7090 (76.0)</td>
<td>6986 (75.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>Angiotensin-II–receptor blocker</td>
<td>1143 (12.2)</td>
<td>1125 (12.1)</td>
<td>0.79</td>
</tr>
<tr>
<td>Cholesterol-lowering drug (statin)</td>
<td>8373 (89.7)</td>
<td>8289 (89.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Calcium-channel inhibitor</td>
<td>2769 (29.7)</td>
<td>2789 (30.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Proton-pump inhibitor</td>
<td>4233 (45.4)</td>
<td>4128 (44.4)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
botic events (14.6% vs. 16.7%, P<0.001); myocardial infarction alone (5.8% vs. 6.9%, P=0.005); and death due to vascular causes (4.0% vs. 5.1%, P=0.001). This pattern was also reflected in a reduction in the rate of death from any cause with ticagrelor (4.5%, vs. 5.9% with clopidogrel; P<0.001). The rate of stroke did not differ significantly between the two treatment groups, although there were more hemorrhagic strokes with ticagrelor than with clopidogrel (23 [0.2%] vs. 13 [0.1%], nominal P=0.10). Concerning our first secondary objective of ascertaining the effect in patients for whom invasive treatment was planned, the rate of the primary end point was also lower with ticagrelor (8.9%, vs. 10.6% with clopidogrel; P=0.003). Among patients who received a stent during the study, the rate of definite stent thrombosis was lower in the ticagrelor group than in the clopidogrel group (1.3% vs. 1.9%, P=0.009).

The results regarding the primary end point did not show significant heterogeneity in analyses of the 33 subgroups, with three exceptions (Fig. 2 in the Supplementary Appendix). The benefit of ticagrelor appeared to be attenuated in patients weighing less than the median weight for their sex (P=0.04 for the interaction), those not taking lipid-lowering drugs at randomization (P=0.04 for the interaction), and those enrolled in North America (P=0.045 for the interaction).

**BLEEDING**

The ticagrelor and clopidogrel groups did not differ significantly with regard to the rates of major
bleeding as defined in the trial (11.6% and 11.2%, respectively; P=0.43) (Fig. 2 and Table 4). There was also no significant difference in the rates of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria (7.9% with ticagrelor and 7.7% with clopidogrel, P=0.57) or fatal or life-threatening bleeding (5.8% in both groups, P=0.70). The absence of a significant difference in major bleeding according to the trial definition was consistent among all subgroups, without significant heterogeneity, except with regard to the body-mass index (P=0.05 for interaction) (Fig. 4 in the Supplementary Appendix). The two treatment groups did not differ significantly in the rates of CABG-related major bleeding or bleeding requiring transfusion of red cells.

### Table 3. Major Efficacy End Points at 12 Months.†

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ticagrelor Group (%)</th>
<th>Clopidogrel Group (%)</th>
<th>Hazard Ratio for Ticagrelor Group (95% CI)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: death from vascular causes, MI, or stroke — no./total no. (%)</td>
<td>864/9333 (9.8)</td>
<td>1014/9291 (11.7)</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Secondary end points — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause, MI, or stroke</td>
<td>901/9333 (10.2)</td>
<td>1065/9291 (12.3)</td>
<td>0.84 (0.77–0.92)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Death from vascular causes, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event</td>
<td>1290/9333 (14.6)</td>
<td>1456/9291 (16.7)</td>
<td>0.88 (0.81–0.95)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>MI</td>
<td>504/9333 (5.8)</td>
<td>593/9291 (6.9)</td>
<td>0.84 (0.75–0.95)</td>
<td>0.005‡</td>
</tr>
<tr>
<td>Death from vascular causes</td>
<td>353/9333 (4.0)</td>
<td>442/9291 (5.1)</td>
<td>0.79 (0.69–0.91)</td>
<td>0.001‡</td>
</tr>
<tr>
<td>Stroke</td>
<td>125/9333 (1.5)</td>
<td>106/9291 (1.3)</td>
<td>1.17 (0.91–1.52)</td>
<td>0.22</td>
</tr>
<tr>
<td>Ischemic</td>
<td>96/9333 (1.1)</td>
<td>91/9291 (1.1)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>23/9333 (0.2)</td>
<td>13/9291 (0.1)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>10/9333 (0.1)</td>
<td>2/9291 (0.02)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Other events — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>399/9333 (4.5)</td>
<td>506/9291 (5.9)</td>
<td>0.78 (0.69–0.89)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Death from causes other than vascular causes</td>
<td>46/9333 (0.5)</td>
<td>64/9291 (0.8)</td>
<td>0.71 (0.49–1.04)</td>
<td>0.08</td>
</tr>
<tr>
<td>Severe recurrent ischemia</td>
<td>302/9333 (3.5)</td>
<td>345/9291 (4.0)</td>
<td>0.87 (0.74–1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>500/9333 (5.8)</td>
<td>536/9291 (6.2)</td>
<td>0.93 (0.82–1.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>TIA</td>
<td>18/9333 (0.2)</td>
<td>23/9291 (0.3)</td>
<td>0.78 (0.42–1.44)</td>
<td>0.42</td>
</tr>
<tr>
<td>Other arterial thrombotic event</td>
<td>19/9333 (0.2)</td>
<td>31/9291 (0.4)</td>
<td>0.61 (0.34–1.08)</td>
<td>0.09</td>
</tr>
<tr>
<td>Death from vascular causes, MI, stroke — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive treatment planned§</td>
<td>569/6732 (8.9)</td>
<td>668/6676 (10.6)</td>
<td>0.84 (0.75–0.94)</td>
<td>0.003‡</td>
</tr>
<tr>
<td>Event rate, days 1–30</td>
<td>443/9333 (4.8)</td>
<td>502/9291 (5.4)</td>
<td>0.88 (0.77–1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>Event rate, days 31–360¶</td>
<td>413/8763 (5.3)</td>
<td>510/8688 (6.6)</td>
<td>0.80 (0.70–0.91)</td>
<td>&lt;0.001‡</td>
</tr>
<tr>
<td>Stent thrombosis — no. of patients who received a stent/ total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>71/5640 (1.3)</td>
<td>106/5649 (1.9)</td>
<td>0.67 (0.50–0.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>Probable or definite</td>
<td>118/5640 (2.2)</td>
<td>158/5649 (2.9)</td>
<td>0.75 (0.59–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Possible, probable, or definite</td>
<td>155/5640 (2.9)</td>
<td>202/5649 (3.8)</td>
<td>0.77 (0.62–0.95)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* The percentages are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have had more than one type of end point. Death from vascular causes included fatal bleeding. Only traumatic fatal bleeding was excluded from the category of death from vascular causes. MI denotes myocardial infarction, and TIA transient ischemic attack.

† P values were calculated by means of Cox regression analysis.

‡ Statistical significance was confirmed in the hierarchical testing sequence applied to the secondary composite efficacy end points.

§ A plan for invasive or noninvasive (medical) management was declared before randomization.

¶ Patients with any primary event during the first 30 days were excluded.
ever, in the ticagrelor group, there was a higher rate of non–CABG-related major bleeding according to the study criteria (4.5% vs. 3.8%, P=0.03) and the TIMI criteria (2.8% vs. 2.2%, P=0.03) (Fig. 3 in the Supplementary Appendix). With ticagrelor as compared with clopidogrel, there were more episodes of intracranial bleeding (26 [0.3%] vs. 14 [0.2%], P=0.06), including fatal intracranial bleeding (11 [0.1%] vs. 1 [0.01%], P=0.02). However, there were fewer episodes of other types of fatal bleeding in the ticagrelor group (9 [0.1%], vs. 21 [0.3%] in the clopidogrel group; P=0.03) (Table 4).

**OTHER ADVERSE EVENTS**

Dyspnea was more common in the ticagrelor group than in the clopidogrel group (in 13.8% of patients vs. 7.8%) (Table 4). Few patients discontinued the study drug because of dyspnea (0.9% of patients in the ticagrelor group and 0.1% in the clopidogrel group).

Holter monitoring was performed for a median of 6 days during the first week in 2866 patients and was repeated at 30 days in 1991 patients. There was a higher incidence of ventricular pauses in the first week, but not at day 30, in the ticagrelor group than in the clopidogrel group (Table 4). Pauses were rarely associated with symptoms; the two treatment groups did not differ significantly with respect to the incidence of syncope or pacemaker implantation (Table 4).

Discontinuation of the study drug due to adverse events occurred more frequently with ticagrelor than with clopidogrel (in 7.4% of patients vs. 6.0%, P<0.001) (Table 2). The levels of creatinine and uric acid increased slightly more during the treatment period with ticagrelor than with clopidogrel (Table 4).

**DISCUSSION**

PLATO shows that treatment with ticagrelor as compared with clopidogrel in patients with acute coronary syndromes significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke. A similar benefit was seen for the individual components of death from vascular causes and myocardial infarction, but not for stroke. The beneficial effects of ticagrelor were achieved without a significant increase in the rate of major bleeding.

The benefits of ticagrelor over clopidogrel were seen in patients who had an acute coronary syndrome with or without ST-segment elevation. Previous trials have shown benefits of clopidogrel in the same clinical settings. The advantages were seen regardless of whether patients had received appropriate initiation of treatment with the
currently recommended higher loading dose of clopidogrel and regardless of whether invasive or noninvasive management was planned.20-25 The treatment effects were the same in the short term (days 0 to 30) and in the longer term (days 31 to 360). This duration of treatment benefit has also been shown with clopidogrel.26 Thus, ticagrelor appears to expand on the previously demonstrated benefits of clopidogrel across the spectrum of acute coronary syndromes.

<table>
<thead>
<tr>
<th>Table 4. Safety of the Study Drugs.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End Point</strong></td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td><strong>Primary safety end points — no./total no. (%)</strong></td>
</tr>
<tr>
<td>Major bleeding, study criteria</td>
</tr>
<tr>
<td>Major bleeding, TIMI criteria‡</td>
</tr>
<tr>
<td>Bleeding requiring red-cell transfusion</td>
</tr>
<tr>
<td>Life-threatening or fatal bleeding, study criteria</td>
</tr>
<tr>
<td>Fatal bleeding</td>
</tr>
<tr>
<td>Nonintracranial fatal bleeding</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
</tr>
<tr>
<td>Fatal</td>
</tr>
<tr>
<td>Nonfatal</td>
</tr>
<tr>
<td><strong>Secondary safety end points — no./total no. (%)</strong></td>
</tr>
<tr>
<td>Non–CABG-related major bleeding, study criteria</td>
</tr>
<tr>
<td>Non–CABG-related major bleeding, TIMI criteria</td>
</tr>
<tr>
<td>CABG-related major bleeding, study criteria</td>
</tr>
<tr>
<td>CABG-related major bleeding, TIMI criteria</td>
</tr>
<tr>
<td>Major or minor bleeding, study criteria</td>
</tr>
<tr>
<td>Major or minor bleeding, TIMI criteria‡</td>
</tr>
<tr>
<td><strong>Dyspnea — no./total no. (%)</strong></td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Requiring discontinuation of study treatment</td>
</tr>
<tr>
<td><strong>Bradykardia — no./total no. (%)</strong></td>
</tr>
<tr>
<td>Pacemaker insertion</td>
</tr>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
<tr>
<td>Heart block</td>
</tr>
<tr>
<td><strong>Holter monitoring — no./total no. (%)</strong></td>
</tr>
<tr>
<td>First week</td>
</tr>
<tr>
<td>Ventricular pauses ≥3 sec</td>
</tr>
<tr>
<td>Ventricular pauses ≥5 sec</td>
</tr>
<tr>
<td>At 30 days</td>
</tr>
<tr>
<td>Ventricular pauses ≥3 sec</td>
</tr>
<tr>
<td>Ventricular pauses ≥5 sec</td>
</tr>
<tr>
<td><strong>Neoplasm arising during treatment — no. of patients/total no. (%)</strong></td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>Malignant</td>
</tr>
<tr>
<td>Benign</td>
</tr>
</tbody>
</table>
The incremental reduction in the risk of coronary thrombotic events (i.e., myocardial infarction and stent thrombosis) through more-intense P2Y12 inhibition with ticagrelor is consistent with similar effects of prasugrel. As noted above, the benefits with ticagrelor were seen regardless of whether invasive or noninvasive management was planned; this issue has not been investigated with other P2Y12 inhibitors. Treatment with ticagrelor was also associated with an absolute reduction of 1.4 percentage points and a relative reduction of 22% in the rate of death from any cause at 1 year. This survival benefit from more-intense platelet inhibition with ticagrelor is consistent with reductions in the mortality rate obtained by means of platelet inhibition with aspirin in patients who had an acute coronary syndrome and with clopidogrel in patients who had myocardial infarction with ST-segment elevation. In contrast, other contemporary trials involving patients with an acute coronary syndrome have not shown significant reductions in the mortality rate with the use of clopidogrel, prasugrel, or glycoprotein IIb/IIIa inhibitors. The improved survival rate with ticagrelor might be due to the decrease in the risk of thrombotic events without a concomitant increase in the risk of major bleeding, as seen with other antithrombotic treatments in patients with an acute coronary syndrome.

Since P2Y12 inhibition with ticagrelor is reversible, the antiplatelet effect dissipates more rapidly than with the thienopyridines, which are irreversible P2Y12 inhibitors. Therefore, less procedure-related bleeding might be expected. Although the rates of major bleeding were not lower with ticagrelor than with clopidogrel, the more-intense platelet inhibition with ticagrelor was not associated with an increase in the rate of any major bleeding. In contrast to the experience with prasugrel, which is also a more effective platelet inhibitor than clopidogrel but is irreversible, there was no increased risk of CABG-related bleeding with ticagrelor. As with prasugrel, non–procedure-related bleeding (spontaneous bleeding), including gastrointestinal and intracranial bleeding, was more common with ticagrelor than with clopidogrel. Although the rare episodes of intracranial bleeding were often fatal, the rates of nonintracranial fatal bleeding, death from vascular causes, and death from any other cause were lower in the ticagrelor group than in the clopidogrel group, resulting in an overall reduction in the mortality rate with ticagrelor.

Dyspnea occurred more frequently with ticagrelor than with clopidogrel. Most episodes lasted less than a week. Discontinuation of the study drug because of dyspnea occurred in 0.9% of patients in the ticagrelor group. Holter monitoring detected more ventricular pauses during

### Table 4. (Continued.)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ticagrelor Group</th>
<th>Clopidogrel Group</th>
<th>Hazard or Odds Ratio for Ticagrelor Group (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in serum uric acid from baseline value — %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 mo</td>
<td>14±46</td>
<td>7±44</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>At 12 mo</td>
<td>15±52</td>
<td>7±31</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1 Mo after end of treatment</td>
<td>7±43</td>
<td>8±48</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>Increase in serum creatinine from baseline value — %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 1 mo</td>
<td>10±22</td>
<td>8±21</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>At 12 mo</td>
<td>11±22</td>
<td>9±22</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1 Mo after end of treatment</td>
<td>10±22</td>
<td>10±22</td>
<td>0.59</td>
<td></td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. Data are shown for patients who received at least one dose of the study drug for events occurring up to 7 days after permanent discontinuation of the study drug. The percentages for the primary and secondary safety end points are Kaplan–Meier estimates of the rate of the end point at 12 months. Patients could have more than one type of end point. CABG denotes coronary-artery bypass grafting.

†Hazard ratios are shown for all safety end points except bleeding requiring red-cell transfusion, for which odds ratios are shown. P values for the odds ratios were calculated with the use of Fisher’s exact test.

‡Major bleeding and major or minor bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria refer to nonadjudicated events analyzed with the use of a statistically programmed analysis in accordance with previously used definitions.
the first week in the ticagrelor group than in the clopidogrel group, but such episodes were infrequent at 30 days and were rarely associated with symptoms. There were no significant differences in the rates of clinical manifestations of bradycardia between the two treatment groups.

The superiority of ticagrelor over clopidogrel with regard to the primary end point, as well as the similarity in rates of major bleeding, was consistent in 62 of 66 subgroups; the differences were significant in the remaining 4 subgroups (P<0.05 for heterogeneity). These findings may have been due to chance, given the large number of tests performed. The difference in results between patients enrolled in North America and those enrolled elsewhere raises the questions of whether geographic differences between populations of patients or practice patterns influenced the effects of the randomized treatments, although no apparent explanations have been found.

In conclusion, in patients who had an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor, as compared with clopidogrel, significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke, without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding.

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APPENDIX

Members of select PLATO committees are as follows (with principal investigators at participating centers and members of other committees listed in the Supplementary Appendix): Executive Committee — Sweden: L. Wallentin (cochair), S. James, I. Ekman; H. Emanuelsson, A. Freij, M. Thorsen; United States: R.A. Harrington (cochair), R. Becker, C. Cannon, J. Horroch; Denmark: S. Husted; Germany: H. Katus; U.K.: A. Skene (statistician), R.F. Storey; France: P.G. Steg; Steering Committee — Italy: D. Ardissino; Austria: P. Aylward; Philippines: N. Babilonia; France: J-P. Bassand; Poland: A. Budaj; Georgia: Z. Chapichadze; Belgium: M.J. Claeyss; South Africa: P. Commroder; the Netherlands: J.H. Cornel, F. Verheugt; Slovenia Republic: T. Duris; China: R. Gao; Mexico: G.C. Armando; Germany: E. Giannitsis; United States: P. Gurbel, R. Harrington, N. Kleiman, M. Sabatine, D. Weaver; Spain: M. Heras; Denmark: S. Husted; Sweden: S. James; Hungary: M. Keltai; Norway: F. Kontny; Greece: D. Kremastinos; Finland: R. Lasila; Israel: B.S. Lewis; Spain: J.L. Sendon; Hong Kong: C. Man Yu; Austria: G. Maurer; Switzerland: B. Meier; Portugal: J. Morais; Brazil: I. Nicolau; Ukraine: A. Nikolaevich Parkhomenko; Turkey: A. Oto; India: P. Pais; Argentina: E. Paolasso; Bulgaria: D. Rave; Malaysia: D.S. Robaayy Zambahari; Russia: M. Ruda; Indonesia: A. Santoso; South Korea: K.-B. Seung; Singapore: L. Soo Teik; Czech Republic: J. Spinar; Thailand: P. Sritara; United Kingdom: R. Storey; Canada: P. Théroux; Romania: M. Vinitsila; Taiwan: D.W. Wu; Data Monitoring Committee — United States: J.L. Anderson (chair), D. DeMets (statistician); the Netherlands: M. Simonsoons; United Kingdom: R. Wilecox; Belgium: F. Van de Werf.

REFERENCES


