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Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and more pronounced platelet inhibition than clopidogrel.

METHODS

In this multicenter, double-blind, randomized trial, we compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with an acute coronary syndrome, with or without ST-segment elevation.

RESULTS

At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). Predefined hierarchical testing of secondary end points showed significant differences in the rates of other composite end points, as well as myocardial infarction alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group, P=0.005) and death from vascular causes (4.0% vs. 5.1%, P=0.001) but not stroke alone (1.5% vs. 1.3%, P=0.22). The rate of death from any cause was also reduced with ticagrelor (4.5%, vs. 5.9% with clopidogrel; P<0.001). No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; P=0.43), but ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, P=0.03), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types.

CONCLUSIONS

In patients who have 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. (ClinicalTrials.gov number, NCT00391872.)

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In patients who have acute coronary syndromes with or without ST-segment elevation, current clinical practice guidelines[1-4] 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,[5,6] an increased risk of bleeding,[7,8] and an increased risk of stent thrombosis and myocardial infarction in patients with a poor response.[9] As compared with clopidogrel, prasugrel, another thienopyridine prodrug, has a more consistent and pronounced inhibitory effect on platelets,[5,6] 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).[10]

Ticagrelor, a reversible and direct-acting oral antagonist of the adenosine diphosphate receptor P2Y12, provides faster, greater, and more consistent P2Y12 inhibition than clopidogrel.[11,12] 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.[13] 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.[14] 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 m^2 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.*

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

Table 1. (Continued.)

Characteristic	Ticagrelor Group	Clopidogrel Group
Risk factors for non–ST-elevation MI — no./total no. (%)¶		
Positive troponin I test	4418/5554 (79.5)	4455/5513 (80.8)
ST-segment depression >0.1 mV	3141/5554 (56.6)	3182/5513 (57.7)
TIMI risk score ≥5	1112/5554 (20.0)	1170/5513 (21.2)

* A positive result on testing for troponin I consisted of a troponin I level of 0.08 μg or more per liter for the first sample taken, as measured at the central laboratory with the use of the Advia Centaur TnI-Ultra Immunoassay (Siemens). ACS denotes acute coronary syndrome, ECG electrocardiographic, MI myocardial infarction, and TIMI Thrombolysis in Myocardial Infarction.
† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
‡ Race was self-reported. "Asian" does not include Indian or Southwest Asian ancestry.
§ This category includes patients with unspecified ACS or no ACS.
¶ Risk factors for non–ST-elevation MI were ascertained for patients with a final ACS diagnosis of non–ST-elevation MI or unstable angina.

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 nonstudy 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.*

Characteristic	Ticagrelor Group (N=9333)	Clopidogrel Group (N=9291)	P Value†
Start of randomized treatment			
Patients receiving treatment — no. (%)	9235 (98.9)	9186 (98.9)	
Time after start of chest pain — hr			0.89
Median	11.3	11.3	
IQR	4.8–19.8	4.8–19.8	
Time after start of hospitalization — hr			0.75
Median	4.9	5.3	
IQR	1.3–18.8	1.4–15.8	
Premature discontinuation of study drug — no. (%)	2186 (23.4)	1999 (21.5)	0.002
Because of adverse event	690 (7.4)	556 (6.0)	<0.001
Because of patient's unwillingness to continue	946 (10.1)	859 (9.2)	0.04
Other reason	550 (5.9)	584 (6.3)	0.27
Adherence to study drug — no. (%)‡	7724 (82.8)	7697 (82.8)	0.89
Exposure to study drug — days			0.11
Median	277	277	
IQR	177–365	181–365	
Clopidogrel administered in hospital before randomization — no. (%)	4293 (46.0)	4282 (46.1)	0.91
Clopidogrel dose given (as study drug or not) within 24 hours before or after randomization — no. (%)			0.65
No loading dose, or missing information	4937 (52.9)	94 (1.0)	
300–375 mg	1921 (20.6)	5528 (59.5)	
600–675 mg	1282 (13.7)	1822 (19.6)	
Other dose	697 (7.5)	1339 (14.4)	
Same dose as that given before index event§	496 (5.3)	508 (5.5)	
Antithrombotic treatment in hospital — no. (%)			
Aspirin			
Before randomization	8827 (94.6)	8755 (94.2)	0.31
After randomization	9092 (97.4)	9056 (97.5)	0.85
Unfractionated heparin	5304 (56.8)	5233 (56.3)	0.49
Low-molecular-weight heparin	4813 (51.6)	4706 (50.7)	0.21
Fondaparinux	251 (2.7)	246 (2.6)	0.89
Bivalirudin	188 (2.0)	183 (2.0)	0.83
Glycoprotein IIb/IIIa inhibitor	2468 (26.4)	2487 (26.8)	0.62
Other medication administered in hospital or at discharge — no. (%)			
Organic nitrate	7181 (76.9)	7088 (76.3)	0.30
Beta-blocker	8339 (89.3)	8336 (89.7)	0.42
ACE inhibitor	7090 (76.0)	6986 (75.2)	0.22
Angiotensin-II–receptor blocker	1143 (12.2)	1125 (12.1)	0.79
Cholesterol-lowering drug (statin)	8373 (89.7)	8289 (89.2)	0.27
Calcium-channel inhibitor	2769 (29.7)	2789 (30.0)	0.61
Proton-pump inhibitor	4233 (45.4)	4128 (44.4)	0.21

Table 2. (Continued.)

Characteristic	Ticagrelor Group (N=9333)	Clopidogrel Group (N=9291)	P Value†
Invasive procedure performed during index hospitalization — no. (%)			
Planned invasive treatment	6732 (72.1)	6676 (71.9)	0.68
Coronary angiography	7599 (81.4)	7571 (81.5)	0.91
PCI			
During index hospitalization	5687 (60.9)	5676 (61.1)	0.83
Within 24 hours after randomization	4560 (48.9)	4546 (48.9)	0.93
Cardiac surgery	398 (4.3)	434 (4.7)	0.19
Invasive procedure performed during study — no. (%)			
PCI	5978 (64.1)	5999 (64.6)	0.46
Stenting	5640 (60.4)	5649 (60.8)	0.61
With bare-metal stent only	3921 (42.0)	3892 (41.9)	0.87
With ≥1 drug-eluting stent	1719 (18.4)	1757 (18.9)	0.40
CABG	931 (10.0)	968 (10.4)	0.32
Time from first dose of study drug to PCI — hr			0.78
Patients with ST-elevation MI			
Median	0.25	0.25	
IQR	0.05–0.75	0.05–0.72	
Patients with non–ST-elevation MI			
Median	3.93	3.65	
IQR	0.48–46.9	0.45–50.8	

* ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass grafting, IQR interquartile range, and PCI percutaneous coronary intervention.
† P values were calculated with the use of Fisher's exact test.
‡ Adherence to the study drug was defined as use of more than 80% of the study medication during each interval between visits, as assessed by the site investigator.
§ Patients who had been receiving clopidogrel before the study were not eligible for a loading dose of the drug at study entry.

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

Table 3. Major Efficacy End Points at 12 Months.*

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

* 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.

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. How-

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.[8,17-19] The advantages were seen regardless of whether patients had received appropriate initiation of treatment with the

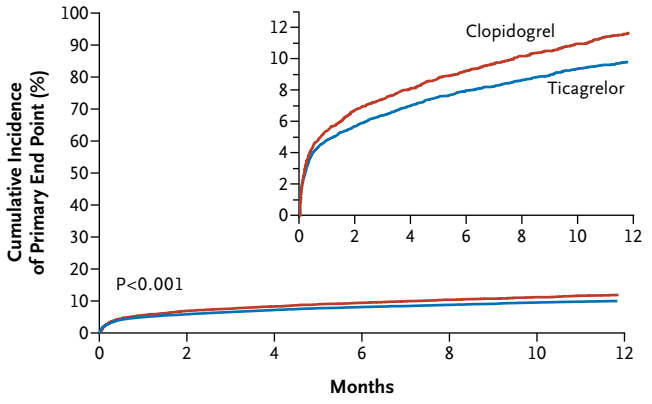

Figure 1. Cumulative Kaplan–Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point.

The primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — occurred significantly less often in the ticagrelor group than in the clopidogrel group (9.8% vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval, 0.77 to 0.92; P<0.001).

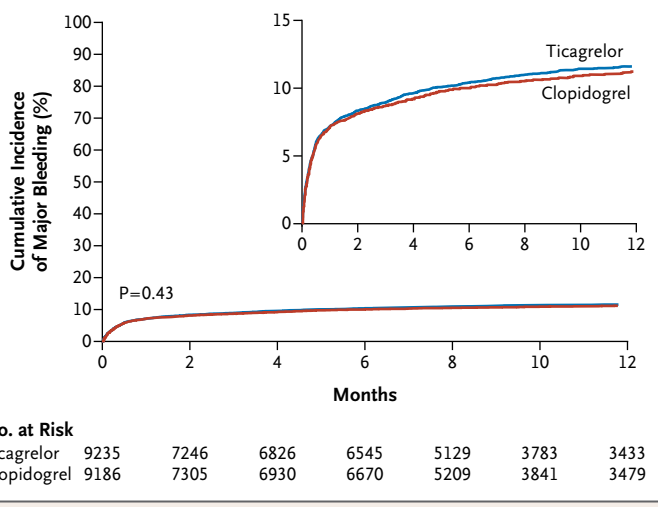

Figure 2. Cumulative Kaplan–Meier Estimates of the Time to the First Major Bleeding End Point, According to the Study Criteria.

The time was estimated from the first dose of the study drug in the safety population. The hazard ratio for major bleeding, defined according to the study criteria, for the ticagrelor group as compared with the clopidogrel group was 1.04 (95% confidence interval, 0.95 to 1.13).

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 4. Safety of the Study Drugs.*

End Point	Ticagrelor Group	Clopidogrel Group	Hazard or Odds Ratio for Ticagrelor Group (95% CI)†	P Value
Primary safety end points — no./total no. (%)				
Major bleeding, study criteria	961/9235 (11.6)	929/9186 (11.2)	1.04 (0.95–1.13)	0.43
Major bleeding, TIMI criteria‡	657/9235 (7.9)	638/9186 (7.7)	1.03 (0.93–1.15)	0.57
Bleeding requiring red-cell transfusion	818/9235 (8.9)	809/9186 (8.9)	1.00 (0.91–1.11)	0.96
Life-threatening or fatal bleeding, study criteria	491/9235 (5.8)	480/9186 (5.8)	1.03 (0.90–1.16)	0.70
Fatal bleeding	20/9235 (0.3)	23/9186 (0.3)	0.87 (0.48–1.59)	0.66
Nonintracranial fatal bleeding	9/9235 (0.1)	21/9186 (0.3)		0.03
Intracranial bleeding	26/9235 (0.3)	14/9186 (0.2)	1.87 (0.98–3.58)	0.06
Fatal	11/9235 (0.1)	1/9186 (0.01)		0.02
Nonfatal	15/9235 (0.2)	13/9186 (0.2)		0.69
Secondary safety end points — no./total no. (%)				
Non–CABG-related major bleeding, study criteria	362/9235 (4.5)	306/9186 (3.8)	1.19 (1.02–1.38)	0.03
Non–CABG-related major bleeding, TIMI criteria	221/9235 (2.8)	177/9186 (2.2)	1.25 (1.03, 1.53)	0.03
CABG-related major bleeding, study criteria	619/9235 (7.4)	654/9186 (7.9)	0.95 (0.85–1.06)	0.32
CABG-related major bleeding, TIMI criteria	446/9235 (5.3)	476/9186 (5.8)	0.94 (0.82–1.07)	0.32
Major or minor bleeding, study criteria	1339/9235 (16.1)	1215/9186 (14.6)	1.11 (1.03–1.20)	0.008
Major or minor bleeding, TIMI criteria‡	946/9235 (11.4)	906/9186 (10.9)	1.05 (0.96–1.15)	0.33
Dyspnea — no./total no. (%)				
Any	1270/9235 (13.8)	721/9186 (7.8)	1.84 (1.68–2.02)	<0.001
Requiring discontinuation of study treatment	79/9235 (0.9)	13/9186 (0.1)	6.12 (3.41–11.01)	<0.001
Bradycardia — no./total no. (%)				
Pacemaker insertion	82/9235 (0.9)	79/9186 (0.9)		0.87
Syncope	100/9235 (1.1)	76/9186 (0.8)		0.08
Bradycardia	409/9235 (4.4)	372/9186 (4.0)		0.21
Heart block	67/9235 (0.7)	66/9186 (0.7)		1.00
Holter monitoring — no./total no. (%)				
First week				
Ventricular pauses ≥3 sec	84/1451 (5.8)	51/1415 (3.6)		0.01
Ventricular pauses ≥5 sec	29/1451 (2.0)	17/1415 (1.2)		0.10
At 30 days				
Ventricular pauses ≥3 sec	21/985 (2.1)	17/1006 (1.7)		0.52
Ventricular pauses ≥5 sec	8/985 (0.8)	6/1006 (0.6)		0.60
Neoplasm arising during treatment — no. of patients/ total no. (%)				
Any	132/9235 (1.4)	155/9186 (1.7)		0.17
Malignant	115/9235 (1.2)	121/9186 (1.3)		0.69
Benign	18/9235 (0.2)	35/9186 (0.4)		0.02

Table 4. (Continued.)

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

* 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.[10]

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.[10] 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[27,28] and with clopidogrel in patients who had myocardial infarction with ST-segment elevation.[22] 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,[8] prasugrel,[10] or glycoprotein IIb/IIIa inhibitors.[29] 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.[30-32]

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,[10] 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,[10] 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.[13] 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

the first week in the ticagrelor group than in the clopidogrel group,[13] 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 bradyarrhythmia 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. Horrow; *Denmark:* S. Husted; *Germany:* H. Katus; *U.K.:* A. Skene (statistician), R.F. Storey; *France:* P.G. Steg; **Steering Committee** — *Italy:* D. Ardissino; *Australia:* P. Aylward; *Philippines:* N. Babilonia; *France:* J.-P. Bassand; *Poland:* A. Budaj; *Georgia:* Z. Chapichadze; *Belgium:* M.J. Claeys; *South Africa:* P. Commerford; *the Netherlands:* J.H. Cornel, F. Verheugt; *Slovak 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. Lassila; *Israel:* B.S. Lewis; *Spain:* J.L. Sendon; *Hong Kong:* C. Man Yu; *Austria:* G. Maurer; *Switzerland:* B. Meier; *Portugal:* J. Morais; *Brazil:* J. Nicolau; *Ukraine:* A. Nikolaevich Parkhomenko; *Turkey:* A. Oto; *India:* P. Pais; *Argentina:* E. Paolasso; *Bulgaria:* D. Raev; *Malaysia:* D.S. Robaayah 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. Vintila; *Taiwan:* D.W. Wu; **Data Monitoring Committee** — *United States:* J.L. Anderson (chair), D. DeMets (statistician); *the Netherlands:* M. Simoons; *United Kingdom:* R. Wilcox; *Belgium:* F. Van de Werf.

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