

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

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Background—We sought to evaluate the effect of potent platelet inhibition after acute coronary syndrome on total (ie, first and recurrent) occurrences of any of the primary outcome events (eg, cardiovascular death, myocardial infarction, and stroke) as well as on other ischemic events, such as urgent revascularization, (severe) recurrent ischemia, transient ischemic attacks, and arterial thrombotic events.

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 end point events versus 1225 for patients on clopidogrel (rate ratio, 0.86; 95% confidence interval, 0.79–0.93; $P=0.003$). The number of additional events was numerically lower for ticagrelor (189 versus 205; $P=0.40$), resulting in a hazard for time to second event/death of 0.80 (95% confidence interval, 0.70–0.90; $P<0.001$) and a number needed to treat of 54. For cardiovascular death/myocardial infarction/stroke/(severe) recurrent ischemia/transient ischemic attack/arterial thrombotic events, total events were fewer with ticagrelor (2030 versus 2290; rate ratio, 0.88; 95% confidence interval, 0.82–0.95; $P<0.001$), with fewer recurrent events with ticagrelor (740 versus 834; $P=0.01$) and a highly significant concurrent reduction in hazard for time to second event or death of 0.83 (95% confidence interval, 0.75–0.91; $P<0.001$). Recurrent PLATO major or Thrombolysis in Myocardial Infarction (TIMI) major non-coronary artery bypass graft 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 with clopidogrel. These types of analyses demonstrate an even greater absolute benefit of ticagrelor over clopidogrel than previously reported.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov/>. Unique identifier: NCT00391872. (*Circulation*. 2013;127:673-680.)

Key Words: antiplatelet agents ■ outcomes assessment

When analyzing the results of a large randomized, controlled trial, patients are typically censored from end point analysis after the first occurrence of any component of the composite primary end points. This practice limits

information to clinicians on the effect of the randomized therapy on subsequent events. Even though information is collected about subsequent (eg, second, third, fourth, etc.) efficacy and safety end point events for the duration

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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.

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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 end point 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 receptor inhibitor prasugrel reduced not only the first occurrence of the composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal 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 adenosine diphosphate 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 (hazard ratio [HR], 0.84; 95% confidence interval [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 2 additional prespecified composite ischemic end points. We also investigated the effect of ticagrelor on recurrent bleeding events.

Methods

The results of the PLATO study have been previously published.⁵ Briefly, the study randomized 18624 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 percutaneous coronary intervention 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 end points, were performed at 1, 3, 6, 9, and 12 months, with another safety visit 1 month after completion of study treatment.

All end points, including recurrent end points, were prespecified and adjudicated by an independent clinical events committee blinded to the randomization.⁵ CVD was defined as cardiovascular, cerebrovascular, or any death without another known cause. Urgent revascularization was defined as ischemia leading to revascularization within the same hospitalization or within 30 days of discharge. In this analysis, we also analyzed 2 prespecified composite ischemic end points 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/urgent

revascularization, the individual components of which were collected and adjudicated during the trial.

All patients who experienced nonfatal 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 nonfatal MI, this was counted toward the primary composite end point of CVD/MI/stroke. If the same patient subsequently had a stroke, the stroke was counted toward 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 (ie, 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 (ie, 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, 1, or multiple events are compared using a χ^2 test for categorical variables and a Kruskal-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 Ying⁶; 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 2 treatment groups was compared with the Wei, Lin, Weissfeld method⁷ to determine a hazard for ticagrelor versus clopidogrel. All analyses were conducted with SAS, version 9.0 (SAS, Cary, NC).

Results

Of the 1888 patients who experienced a primary end point event during follow-up for 6 to 12 months, 1570 developed only 1 event, but 318 patients experienced multiple occurrences of the composite end point of cardiovascular death/MI/stroke. Table 1 shows a graded increase in the number of comorbidities and cardiac risk factors observed among the respective patients with none, 1, and multiple events. Specifically, those with multiple events were more likely to be older or have diabetes mellitus, a previous 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 ST elevation myocardial infarction at study entry were more likely to experience no additional CVD/MI/stroke events during the trial whereas those with non-ST elevation myocardial infarction were more likely to experience multiple events ($P < 0.001$).

Efficacy

As has been already reported, the first occurrence of the primary end point 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.⁶ In addition to the first occurrence, the hazard for the time to second occurrence of this composite end point 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 versus

Table 1. Baseline Characteristics of Patients With No Events, A Single Event, or Multiple CVD/MI/Stroke Events

	None (n=16 736)	Single (n=1570)	Multiple (n=318)	P Value*
Age, y±SD	62 ± 11	66 ± 11	67 ± 11	<0.001
Male sex, n (%)	12 055 (72.0)	1080 (68.8)	201 (63.2)	<0.001
Weight, kg±SD	81 ± 16	78 ± 16	76 ± 16	<0.001
Race				<0.001
White, %	92.1	89.3	84.9	
Black, %	1.2	1.8	1.9	
Asian, %	5.7	7.1	10.1	
Other, %	1.1	1.8	3.1	
Hypertension, n (%)	10 788 (64.5)	1145 (72.9)	250 (78.6)	<0.001
Dyslipidemia, n (%)	7742 (46.3)	786 (50.1)	161 (50.6)	0.006
Diabetes mellitus, n (%)	4000 (23.9)	539 (34.3)	123 (38.7)	<0.001
Current/previous smoking, n (%)	10 282 (61.5)	892 (56.8)	180 (56.6)	<0.001
Previous MI, n (%)	3253 (19.4)	446 (28.4)	125 (39.3)	<0.001
Previous CABG, n (%)	893 (5.3)	169 (10.8)	44 (13.8)	<0.001
CrCl <60 mL/min, n (%)	2644 (15.8)	482 (30.7)	111 (34.9)	<0.001
Index ACS: STEMI, n (%)	6402 (38.3)	527 (33.7)	97 (30.6)	<0.001
Index ACS: non-STEMI, n (%)	7009 (42.0)	778 (49.8)	168 (53.0)	<0.001
Troponin + at entry, n (%)	13 472 (80.5)	1,340 (85.4)	277 (87.1)	<0.001
Randomized to ticagrelor, n (%)	8456 (50.6)	714 (45.5)	154 (48.4)	<0.001

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; MI, myocardial infarction; and STEMI, ST elevation myocardial infarction.

*P value from χ^2 test (categorical variables) or Kruskal-Wallis test (continuous variables) across the 3 categories.

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 versus 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 (ie, not including first events) were similarly reduced (740 versus 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 end point events per patient of this ischemic end point with ticagrelor (Figure 2B), resulting in a NNT for this ischemic end point of 35, and fewer total events in this group (2030 versus 2290; $P<0.001$; Figure 2A).

Regarding the other composite ischemic end point of CVD/MI/Stroke/urgent revascularization, there were similar findings with superior efficacy of ticagrelor. Total events occurred less frequently with ticagrelor compared with clopidogrel (1325 versus 1515; $P<0.001$; Figure 3a) resulting in a rate ratio of 0.87 (95% CI, 0.81 versus 0.94; $P<0.001$) and a NNT of 47. For this end point, 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 were analyzed on a per-protocol basis (Table I in the online-only Data Supplement).

Safety

With respect to safety end points, 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 with the first occurrences in both ticagrelor and clopidogrel arms (70 versus 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 versus 1208 for ticagrelor and clopidogrel), with rate ratio 1.01, $P=0.83$ for total events; and 106 versus 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 end point, with no difference in additional bleeding events in either the ITT cohort (228 versus 226 events; rate ratio, 1.00; $P=0.96$) or the on-treatment cohort (168 versus 162 events; rate ratio, 1.03; $P=0.78$).

Analyzing TIMI major non-CABG bleeding end points, in the on-treatment cohort, there were statistically more total

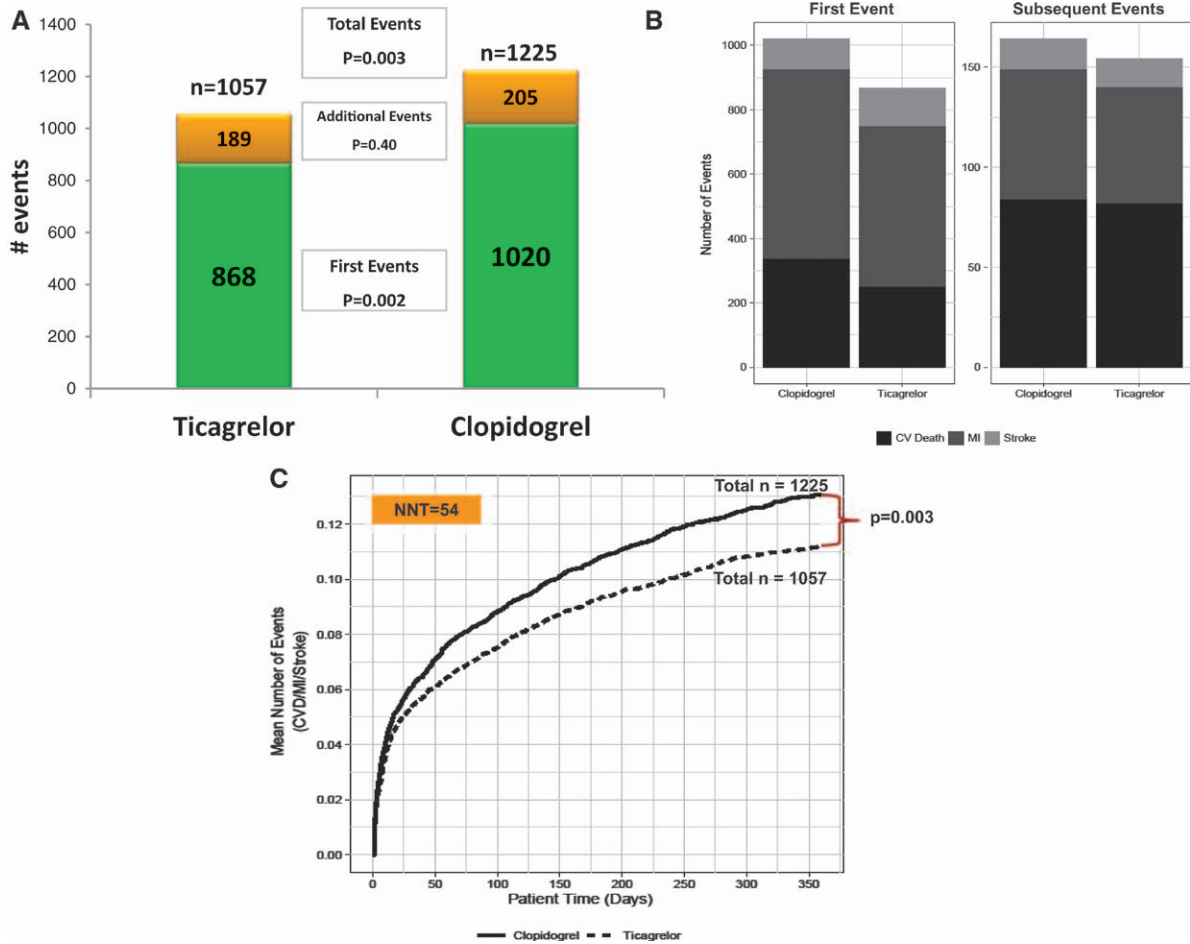


Figure 1. **A**, First (in green), additional (in yellow), and total events for the composite end points of CVD/MI/stroke demonstrated fewer first and total events with ticagrelor. **B**, Number of first and subsequent events (by the specific type of event) for the components of the primary end point; 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 article text 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. CVD indicates cardiovascular death; MI, myocardial infarction; NNT, number needed to treat; and WLW, Wei, Lin, Weissfeld method.

bleeding events (234 versus 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 end point (221 versus 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 versus 227 events; $P=0.10$). However, although first occurrences

Table 2. Time From Randomization to First Event, Time From Randomization to Second Event Or Death, Total Number of Events, Depicted as Hazard Ratios or Risk Ratios (95% CIs) and the Number Needed to Treat to Prevent One Event

Outcome	Time to 1 st Event	Time to 2 nd Event or Death	Total No. of Events	NNT
CVD, MI, stroke	HR 0.84 (0.77–0.92) $P<0.001$	HR 0.80 (0.70–0.90) $P<0.001$	RR 0.86 (0.79–0.93) $P<0.001$	54
CVD, MI, stroke, SRI, RI, TIA, ATE	HR 0.88 (0.82–0.95) $P<0.001$	HR 0.83 (0.75–0.91) $P<0.001$	RR 0.88 (0.83–0.94) $P<0.001$	35
CVD, MI, stroke, UR	HR 0.86 (0.79–0.93) $P<0.001$	HR 0.80 (0.71–0.91) $P<0.001$	RR 0.87 (0.81–0.94) $P<0.001$	47

ATE indicates arterial thrombosis; CI, confidence interval; CVD, cardiovascular death; HR, hazard ratio; MI, myocardial infarction; NNT, number needed to treat; RI, recurrent ischemia; RR, risk ratio; SRI, severe recurrent ischemia; TIA, transient ischemic attack; and UR, urgent revascularization.

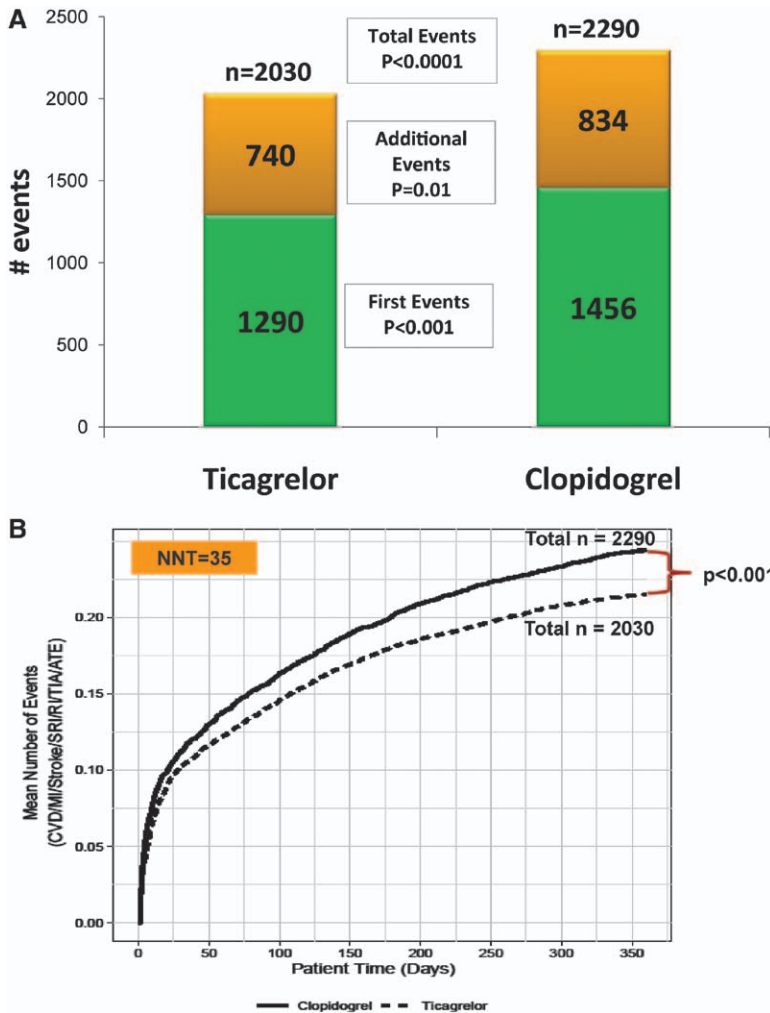


Figure 2. A, First (green), additional (yellow), and total events for the composite end point of CVD/MI/Stroke/SRI/RI/TIA/ATE show fewer events with ticagrelor. B, Mean number of CVD/MI/Stroke/SRI/RI/TIA/ATE events per patient was lower during the trial in the ticagrelor arm compared with clopidogrel. ATE indicates arterial thrombosis; CVD, cardiovascular death; MI, myocardial infarction; NNT, number needed to treat; RI, recurrent ischemia; SRI, severe recurrent ischemia; and TIA, transient ischemic attack.

of bleeding increased with ticagrelor, recurrent bleeding events were uncommon and similar by treatment for both the safety cohort (13 versus 11; $P=0.69$) as well as the ITT cohort (18 versus 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%). After 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 end point 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

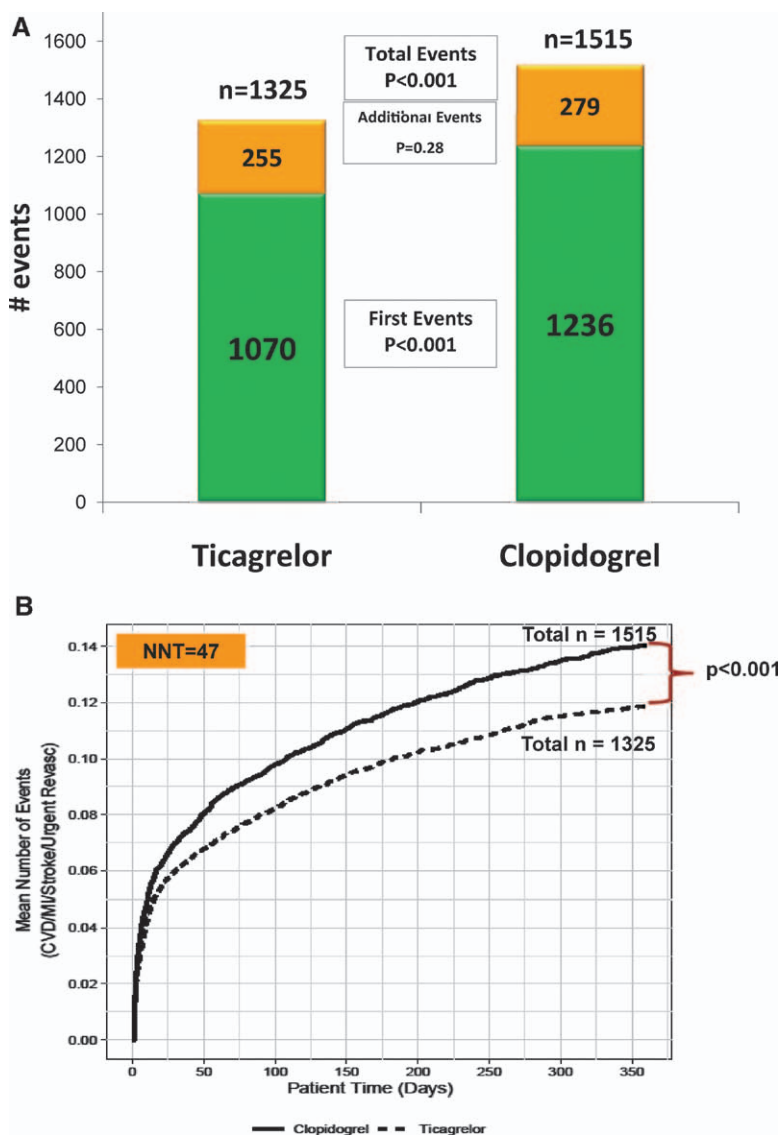


Figure 3. A, First (green), additional (yellow), and total events for the composite end points of CVD/MI/Stroke/UR demonstrated fewer first and total events with ticagrelor. B, Mean number of CVD/MI/Stroke/UR events per patient was lower during the trial in the ticagrelor arm compared with clopidogrel. CVD indicates cardiovascular death; MI, myocardial infarction; NNT, number needed to treat; and UR, urgent revascularization.

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 end point, as well as 2 additional prespecified composite ischemic end points. Based on these total event analyses, we report a NNT of 54 to prevent 1 occurrence of CVD/MI/stroke and even lower numbers (NNT=35 and NNT=47) for the reduction of the other expanded ischemic end points. This effect of acute and long-term treatment with ticagrelor compared with 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 versus pravastatin 40 mg).¹¹

Although the efficacy of potent platelet inhibition was sustained, recurrent bleeding with continued therapy was very infrequent after 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 versus 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% to 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 with 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 versus clopidogrel,^{1,12} and of intensive statin therapy versus 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 Wei, Lin, Weissfeld method survival analysis for recurrent events has

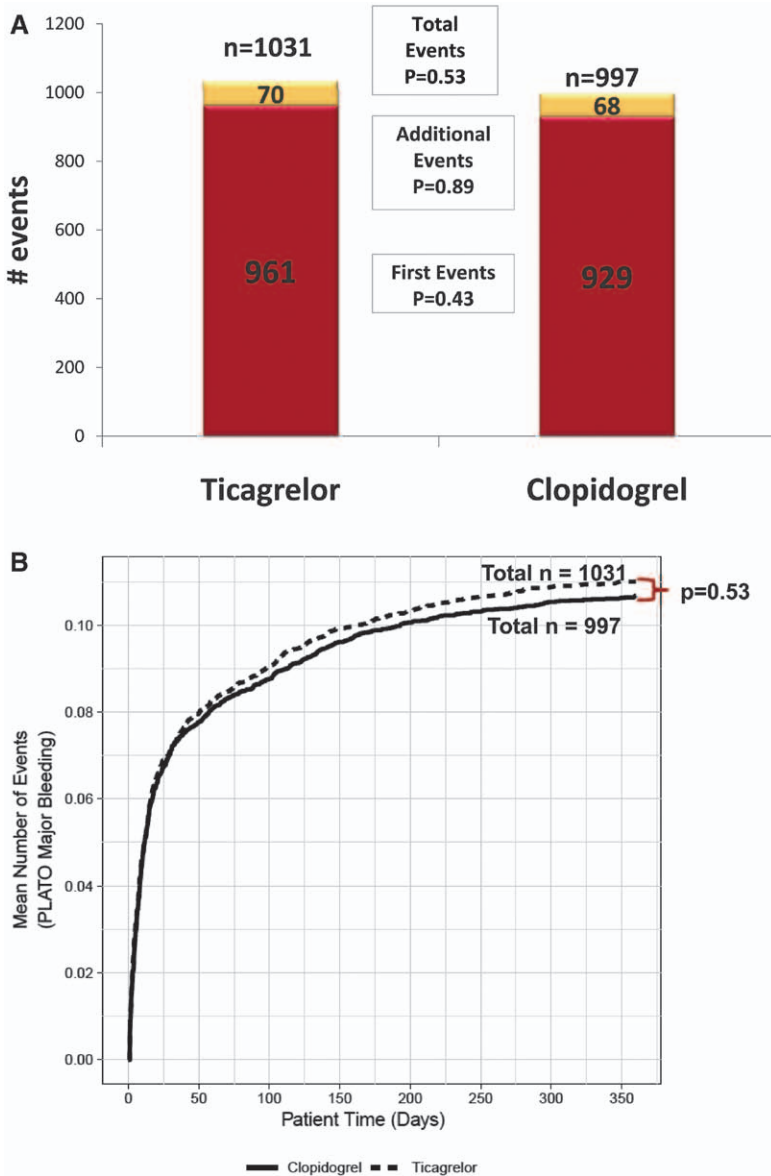


Figure 4. First (in red), additional (in yellow), and total (A) and mean number (B) of PLATO major bleeding events. PLATO indicates PLATelet inhibition and patient Outcomes (PLATO) study.

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 (ie, 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 end points such as CVD/MI/Stroke, where recurrent events are relatively infrequent compared with more comprehensive composite ischemic end points, 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 after 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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Disclosures

Dr Kohli reports honoraria from serving on an advisory board for Daiichi-Sankyo. Dr Wallentin reports research grants from AstraZeneca, Merck/Schering-Plow, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, and GlaxoSmithKline; being a consultant for Merck/Schering-Plow, Regado Biosciences, Evolva, Protola, C.S.L. Behring, Athera Biotechnologies, Boehringer-Ingelheim, AstraZeneca, GlaxoSmithKline, and Bristol-Myers Squibb/Pfizer; lecture fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Schering-Plow; and honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Schering-Plow/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, and Abbott Vascular; and research nd grants paid to Institution from Bristol Myers Squibb, Sanofi-Aventis, GlaxoSmithKline, Otsuka, Eli Lilly Co, Daiichi Sankyo Inc, The Medicines Company, Portola, Accumetrics, Schering-Plow, AstraZeneca, 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 receiving research grants and 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 receiving institutional research grant and 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, and Pfizer, but all funds are donated to charity. He is a clinical Advisor, and holds equity in Automedics Medical Systems.

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CLINICAL PERSPECTIVE

We sought to evaluate the effect of potent platelet inhibition after acute coronary syndrome on total (ie, first and recurrent) occurrences of any of cardiovascular event. In the PLATelet inhibition and patient Outcomes (PLATO) study involving 18 624 patients, treatment with the more potent agent ticagrelor, as compared with clopidogrel, reduced not only the first occurrence but also repeated cardiovascular events. Ticagrelor treatment is associated with a slightly increased risk of having a first non-coronary artery bypass graft 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.