Ticagrelor Compared With Clopidogrel by Geographic Region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial

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Background—In the Platelet Inhibition and Patient Outcomes (PLATO) trial, a prespecified subgroup analysis showed a significant interaction between treatment and region ($P=0.045$), with less effect of ticagrelor in North America than in the rest of the world.

Methods and Results—Reasons for the interaction were explored independently by 2 statistical groups. Systematic errors in trial conduct were investigated. Statistical approaches evaluated the likelihood of play of chance. Cox regression analyses were performed to quantify how much of the regional interaction could be explained by patient characteristics and concomitant treatments, including aspirin maintenance therapy. Landmark Cox regressions at 8 time points evaluated the association of selected factors, including aspirin dose, with outcomes by treatment. Systematic errors in trial conduct were ruled out. Given the large number of subgroup analyses performed and that a result numerically favoring clopidogrel in at least 1 of the 4 prespecified regions could occur with 32% probability, chance alone cannot be ruled out. More patients in the United States (53.6%) than in the rest of the world (1.7%) took a median aspirin dose ≥300 mg/d. Of 37 baseline and postrandomization factors explored, only aspirin dose explained a substantial fraction of the regional interaction. In adjusted analyses, both Cox regression with median maintenance dose and landmark techniques showed that, in patients taking low-dose maintenance aspirin, ticagrelor was associated with better outcomes compared with clopidogrel, with statistical superiority in the rest of the world and similar outcomes in the US cohort.

Conclusions—The regional interaction could arise from chance alone. Results of 2 independently performed analyses identified an underlying statistical interaction with aspirin maintenance dose as a possible explanation for the regional difference. The lowest risk of cardiovascular death, myocardial infarction, or stroke with ticagrelor compared with clopidogrel is associated with a low maintenance dose of concomitant aspirin.

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Key Words: aspirin ■ acute coronary syndrome ■ myocardial infarction ■ outcomes

In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor prevented the composite of cardiovascular death, myocardial infarction (MI), and stroke better than clopidogrel in a broad acute coronary syndrome (ACS) population without increased risk of overall major bleeding.[1–3] Preplanned exploratory analyses examined the variation in the treatment effect in relation to 31 prespecified demographic and patient characteristics. These analyses revealed nominally significant treatment interactions in 3 baseline subgroups: weight by sex ($P=0.038$), use of lipid-lowering therapy at randomization ($P=0.039$), and geographic region ($P=0.045$), the last prospectively defined as North America; Europe, the Middle East, and Africa; Asia and Australia; and Central and South America. Clopidogrel was associated with a nonsignificant trend of better outcome for North America alone, whereas ticagrelor was associated with better outcome in the other regions combined (rest of world [ROW]).[2]

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The results for weight by sex and lipid-lowering therapy, although with similar interaction significance levels, did not

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exhibit qualitative differences and have less clinical relevance. Therefore, additional exploratory analyses were performed to identify potential explanations for the observed region-by-treatment interaction.

Methods

The PLATO trial design, patient population, study protocol procedures, outcome definitions, and trial results have been published.[1–3] The protocol was approved by appropriate national and institutional regulatory authorities and ethics committees, and all participants provided written informed consent. Patients with a new diagnosis of ACS randomly received double-blind ticagrelor or clopidogrel for 6 to 12 months. The protocol specified maintenance treatment with open-label aspirin 75 to 100 mg/d except when contraindicated or not tolerated; this followed a single loading dose (160 to 500 mg allowed, ≤325 mg preferred) for those patients not receiving aspirin just before randomization.[4] After coronary stenting, the protocol allowed 325 mg/d aspirin for ≤6 months.[5] Each treating physician determined a patient's aspirin dose, which was recorded at every study visit.

The observed regional interaction was driven by an interaction of randomized treatment with 78% of North American patients in the United States compared with the ROW patients ($P=0.01$ versus $P=0.045$ for interaction using North America), so these analyses focus on the comparison of the United States and the ROW, with Canadian patients included in the ROW group. The source and nature of the interaction were independently evaluated in exploratory analyses performed by teams from the sponsor and from the Duke Clinical Research Institute. The PLATO data set was stored at the sponsor, the Duke Clinical Research Institute, the Uppsala Clinical Research Center, and the Nottingham Clinical Research Center.

The AstraZeneca team designed and performed the following analyses; the methodology was reviewed by the Duke Clinical Research Institute team. The possibility of systematic errors in trial conduct was explored by interviews with personnel at the largest US sites, by examination of drug supply records and evaluation of ticagrelor plasma levels in patients, and by comparison of dyspnea incidence, a ticagrelor-associated effect observed in the Dose Confirmation Study Assessing Anti-Platelet Effects of AZD6140 vs. Clopidogrel in Non–ST-Segment Elevation Myocardial Infarction-2 (DISPERSE-2) trial.[6] The impact of study drug discontinuation on the regional interaction was investigated by analyzing the primary efficacy outcome, censoring patients at the time of eventual permanent study drug discontinuation.

The role of the play of chance was assessed. Assuming the actual distribution of events and patients enrolled across the countries and an overall hazard ratio (HR) of 0.84, probabilities of various scenarios were calculated. Calculation of the probability of observing a numerically positive HR in each region came from the overall result and number of events in that region. Multiplying these probabilities across the 4 regions gives the probability of no region delivering a numerically positive result favoring clopidogrel; 1 minus this probability is the probability of observing a result numerically favoring clopidogrel in at least 1 region. Calculation of the probability of observing at least 1 statistically significant treatment interaction by chance alone among the original 31 prespecified baseline factors came from 5000 simulations of a multivariate normal distribution with assumed correlation levels among the 31 tests ranging from 0.0 to 0.9999. A correlation of 0.95 warranted an adjusted significance level of 0.02.

Important baseline characteristics and patient management were evaluated by examination of 31 prespecified and 6 postrandomization variables (see Appendix I in the online-only Data Supplement). The 31 prespecified variables were identified before unblinding in the statistical analysis plan to support exploratory analyses for consistency of the overall treatment effect. To explain a meaningful fraction of the region-by-treatment interaction, a candidate factor must simultaneously have a strong qualitative interaction with randomized treatment for the primary end point and be strongly imbalanced between the United States and the ROW.

The effect modifier analysis of the 37 variables was achieved as follows: First, a Cox regression analysis with covariate terms for treatment, region (United States versus ROW), and treatment-by-region interaction was performed. Second, for each of the 37 variables in turn, the analysis was expanded to include a given variable and its interaction with treatment as covariates. If, in the second analysis, the treatment-by-region interaction was no longer significant, then the introduced variable may be responsible for the observed region-by-treatment interaction. In addition, the percentage decrease in the regression coefficient for treatment-by-region interaction from the first to the second analysis was taken as a measure of the degree to which that variable explained the United States–ROW treatment interaction. Results of these analyses were supported by multivariate Cox regression analyses, which gave the same conclusions.

Because preliminary evaluation of the data showed that aspirin dose was strongly imbalanced between US and ROW patients, daily aspirin dose was expressed in several ways in the Cox regression analyses. In line with guidelines specifying a higher loading than maintenance dose, day 1 loading aspirin dose was separated from the subsequent lower aspirin maintenance dose. Aspirin maintenance dose was defined 3 ways: (1) based on all aspirin given between the start of study drug and the primary event/censoring in patients taking aspirin for at least 5 days; (2) identical to 1 except in all patients taking aspirin at least 2 days; and (3) based on aspirin doses from day 2 to the earliest of cessation of randomized therapy or primary event/censoring. Median aspirin dose was used to describe the average maintenance dose for a patient. Definition 3 is considered the most clinically meaningful because it includes all randomized patients with aspirin maintenance doses taken concomitantly with randomized therapy; aspirin doses taken after a patient stopped randomized treatment or reached the primary end point are not included.

Frequency distribution plots of maintenance aspirin dose using definition 3 revealed 3 distinct groups: patients receiving median ≤100 mg/d, those receiving ≥300 mg/d, and those receiving intermediate doses. Treatment effects, in terms of HRs and 95% confidence intervals (CIs), were provided for US and ROW patients receiving median aspirin doses in those categories.

The Duke Clinical Research Institute team performed a series of landmark analyses to calculate the primary efficacy outcome HRs for ticagrelor compared with clopidogrel by region (United States or ROW), adding, individually, 5 postrandomization factors (revascularization, aspirin dose ≥300 mg/d, β-blocker, proton pump inhibitor, or lipid-lowering agent) at each of 8 landmark dates: at randomization and 2, 4, 9, 30, 60, 90, and 180 days later. Each model contained terms for treatment, region (United States or ROW), the selected factor included as a covariate, and the 3 two-way interactions. Medication use was defined as that reported on the landmark date. Adjusted models adding baseline factors known to be predictors of clinical outcomes were explored.[7,8] The landmark models were used to compute, at each landmark date, the HR of ticagrelor compared with clopidogrel by region and for the candidate factor. For aspirin, a simplified model including treatment and aspirin dose and the interaction was used to derive HRs for low compared with high aspirin dose for patients receiving ticagrelor and clopidogrel. The effect modifier analysis was run using the day 4 landmark cohort, the first 27 variables in Appendix I, and the aspirin dose taken on day 4, a point chosen because it likely represents a time by which the maintenance aspirin dose would have been implemented. Similar results for the effect modifier analysis were generated by use of the day 2 and day 9 landmark cohorts (data not shown).

All exploratory analyses used SAS version 9.2 and report nominal significance levels without adjustment for multiplicity.

Results

Assessments of trial conduct revealed no differences between the United States and the ROW. The US site interviews indicated a good understanding of and adherence to the trial protocol and procedures. An audit of interactive voice re-

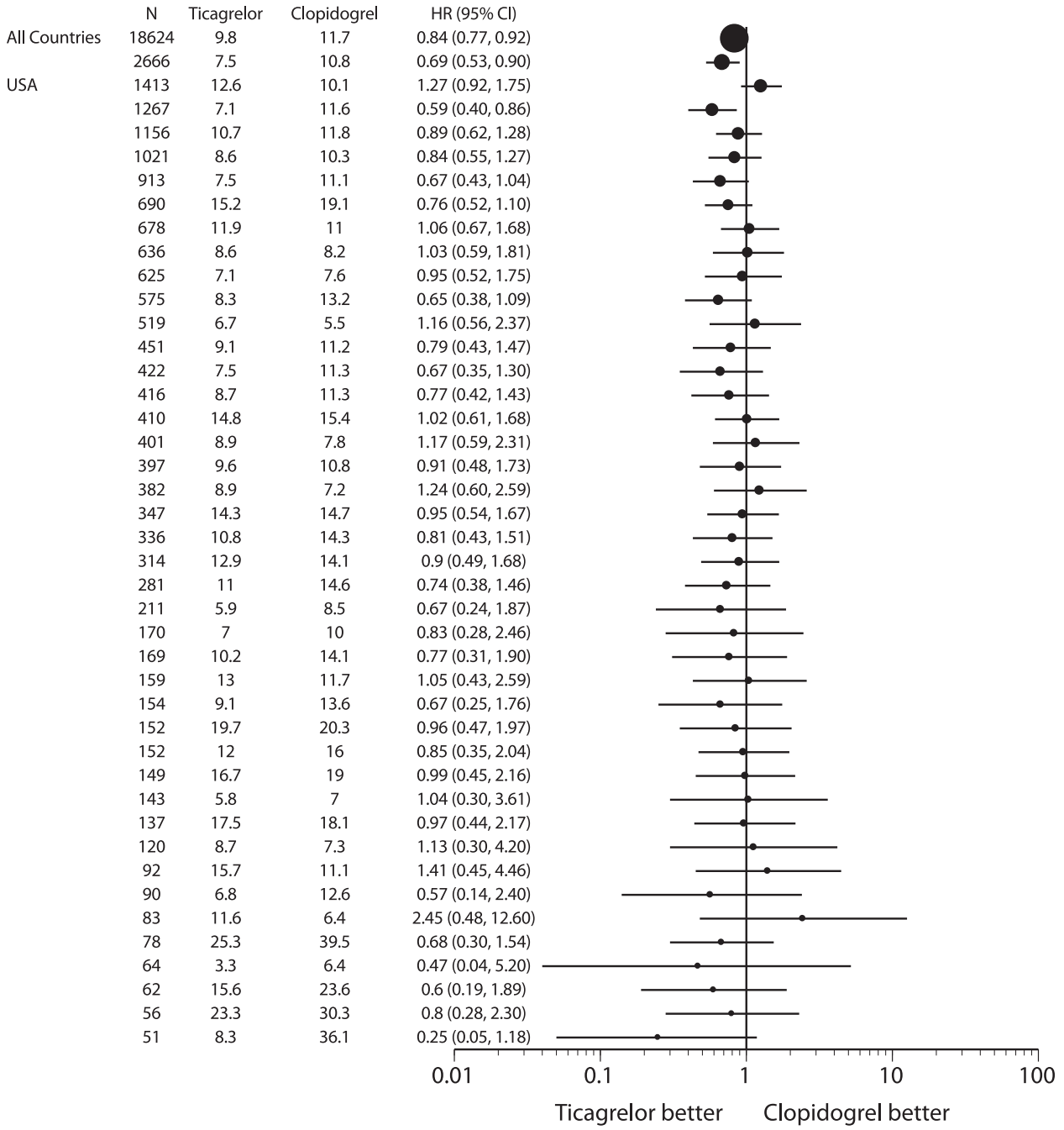

Figure 1. Hazard ratios (HR; ●) and associated 95% confidence intervals (CI) comparing ticagrelor and clopidogrel for the primary efficacy outcome for overall trial (topmost row) and for each of the 43 participating countries ordered by the number (N) of randomized patients.

sponse systems documentation, study batch numbers, and randomization codes indicated that US patients received the proper batches of study drug. Pharmacokinetic substudy samples of US patients in the ticagrelor group contained ticagrelor in their plasma, ruling out a drug swap error in packaging. The United States and ROW exhibited similar data quality, with 68 and 51 queries per patient, respectively.

The US patients had less adherence to randomized treatment drug, defined as >80% compliance at each visit, compared with the ROW patients (62.0% versus 84.7%) and increased overall incidence of study drug discontinuation (31.4% versus 22.0%) with similar rates by treatment group. Primary efficacy outcome results by region, when restricted to patients who permanently discontinued study drug and with censoring at that time, were similar to the entire cohort (HRs, 1.33 for the United States [1.27 for the entire cohort] and 0.84 for the ROW in both cases). Ticagrelor patients reported dyspnea more frequently than clopidogrel patients in both the United States (22% versus 10%) and the ROW (14% versus 8%), suggesting no systematic drug packaging error. Investigators identified potential primary events for adjudication with slightly increased frequency in the United States

compared with the ROW for both ticagrelor (21% and 14%, respectively) and clopidogrel (19% and 16%), suggesting no region-by-treatment bias in event reporting.

Regarding the play of chance, the probability of observing at least 1 false-positive ($P<0.05$) treatment interaction by chance alone among the 31 prespecified baseline variables is 79% if the interaction tests between these variables and randomized treatment are considered to be independent. The corresponding adjusted P value applicable to declare significance would be 0.002. If uniformly correlated with $r=0.75$, for example, the probability of at least 1 false-positive interaction test would be 30%, and the corresponding adjusted P value applicable would be 0.007. Furthermore, given the overall result and distribution of patients and events across regions, the probability of observing a result that numerically favors clopidogrel in at least 1 of the 4 regions would be 32%, and a result numerically favoring clopidogrel in the United States while favoring ticagrelor in the other 3 regions is 10%. The observed HRs for the primary outcome for each country are shown in Figure 1. The HR exceeded 1.0 in 12 countries (28%) and 1.25 in 3 countries (7%). Given the distribution of events across countries and a common HR of 0.84, an HR >1 would be expected in 13 countries and an HR >1.25 would be expected in 6 countries.

Table 1 shows the baseline demographics and clinical characteristics for US and ROW patients. Results for the primary efficacy outcome, its individual components, all-cause mortality, and bleeding outcomes are shown in Table 2.

Results of analyses using the median maintenance dose of aspirin indicate that aspirin maintenance dose could account for 80% to 100% of the observed regional interaction (Figure 2A). None of the other candidate variables explained the regional interaction effect sufficiently to render it statistically nonsignificant. The landmark approach using the aspirin dose taken on day 4 explained ≈40% of the interaction effect (Figure 2B).

Figure 3 shows adjusted HRs for the primary efficacy outcome by region and aspirin maintenance dose. Point estimates of the HRs are similar within dose categories regardless of region, although CIs are wide. For both regions, low-dose maintenance aspirin had lower event rates with ticagrelor. Pooling these results for the overall cohort yields an HR of 1.45 (95% CI, 1.01 to 2.09) favoring clopidogrel for maintenance aspirin dose ≥300 mg and an HR of 0.77 (95% CI, 0.69 to 0.86) favoring ticagrelor for a maintenance aspirin dose ≤100 mg. The interaction between aspirin dose category and treatment is significant at $P=0.00006$. Figure 4 displays the time course of the primary efficacy outcome by treatment and daily maintenance aspirin dose <300 and ≥300 mg. The lowest event rate occurred with ticagrelor in combination with <300-mg/d maintenance dose of aspirin and the highest event rate with ticagrelor with high-dose aspirin. The event rates in patients receiving clopidogrel were similar between those treated with low and those treated with higher doses of aspirin.

In landmark analyses for the factors revascularization, β-blocker, proton pump inhibitor, and lipid-lowering agents, including the factor did not increase the treatment-by-region interaction significance level to ≥0.05 (data not shown).

Table 1. Baseline Characteristics of Patients Enrolled in the United States and the Rest of the World

	United States (n=1413)	Rest of World (17 211)
Age, y*	61 (53–70)	62 (54–71)
Female sex, n (%)	406 (28.7)	4882 (28.4)
Race, n (%)		
White	1262 (89.3)	15 815 (91.9)
Black	137 (9.7)	92 (0.5)
Asian	9 (0.6)	1087 (6.3)
Other	5 (0.4)	216 (1.3)
Weight, kg*	87 (75–100)	80 (70–89)
Body mass index, kg/m^2*	29.1 (25.7–33.1)	27.3 (24.7–30.2)
Hypertension, n (%)	1000 (70.8)	11 183 (65.0)
Dyslipidemia, n (%)	957 (67.8)	7732 (45.0)
Angina pectoris, n (%)	575 (40.7)	7783 (45.3)
Prior MI, n (%)	387 (27.4)	3437 (20.0)
Prior PCI, n (%)	415 (29.4)	2077 (12.1)
Prior coronary artery bypass graft, n (%)	236 (16.7)	870 (5.1)
Chronic obstructive pulmonary disease, n (%)	178 (12.6)	907 (5.3)
Smoking, n (%)		
Nonsmoker	416 (29.5)	6840 (39.8)
Ex-smoker	481 (34.1)	4195 (24.4)
Habitual smoker	515 (36.5)	6163 (35.8)
Diabetes mellitus, n (%)	472 (33.4)	4190 (24.4)
Asthma, n (%)	100 (7.1)	432 (2.5)
History of dyspnea, n (%)	359 (25.4)	2411 (14.0)
Family history of cardiovascular disease, n (%)	742 (52.7)	5207 (30.3)
Congestive heart failure, n (%)	106 (7.5)	944 (5.5)
Peripheral arterial disease, n (%)	130 (9.2)	1014 (5.9)
STEMI, n (%)	222 (15.7)	6804 (39.6)
Killip class, n (%)		
I	1361 (96.5)	15 645 (91.1)
II	45 (3.2)	1357 (7.9)
III–IV	5 (0.3)	167 (1.0)
Persistent ST-segment elevation, n (%)	217 (15.4)	6791 (39.5)
ST-segment depression (≥1 mm), n (%)	450 (32.0)	9036 (52.6)
T-wave inversion, n (%)	342 (24.3)	5603 (32.6)
Troponin, n (%)		
Positive	1176 (83.2)	13 913 (80.8)
Negative	171 (12.1)	2797 (16.3)
Missing	66 (4.7)	501 (2.9)
Systolic blood pressure, mm Hg*	131 (116–146)	133 (120–150)
Diastolic blood pressure, mm Hg*	75 (66–86)	80 (70–90)
Heart rate, bpm*	71 (62–80)	74 (65–84)
β-blockers, n (%)	1142 (80.9)	12 169 (70.8)
Time from index event to study drug, h*	16.7 (8.8–23.0)	10.8 (4.6–19.4)

MI indicates myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

*Median (first to third quartiles).

Table 2. Clinical Events Committee–Adjudicated Primary Efficacy End Points and Bleeding in the United States and the Rest of the World by Treatment

		Ticagrelor (n=9333)			Clopidogrel (n=9291)				
End Point	Region	n	Patients With Events, n (%)	KM, %	n	Patients With Events, n (%)	KM, %	HR (95% CI)	*P*
Cardiovascular death/MI*/stroke	US	707	84 (11.9)	12.6	706	67 (9.5)	10.1	1.27 (0.92–1.75)	0.1459
	ROW	8626	780 (9.0)	9.6	8585	947 (11.0)	11.8	0.81 (0.74–0.90)	<0.0001
Cardiovascular death	US	707	24 (3.4)	3.7	706	19 (2.7)	2.7	1.26 (0.69–2.31)	0.4468
	ROW	8626	329 (3.8)	4.0	8585	423 (4.9)	5.3	0.77 (0.67–0.89)	0.0005
MI*	US	707	64 (9.1)	9.6	706	47 (6.7)	7.2	1.38 (0.95–2.01)	0.0956
	ROW	8626	440 (5.1)	5.5	8585	546 (6.4)	6.9	0.80 (0.70–0.90)	0.0004
Stroke	US	707	7 (1.0)	1.0	706	4 (0.6)	0.6	1.75 (0.51–5.97)	0.3730
	ROW	8626	118 (1.4)	1.5	8585	102 (1.2)	1.3	1.15 (0.88–1.50)	0.2964
All-cause mortality	US	707	28 (4.0)	4.2	706	24 (3.4)	3.6	1.17 (0.68–2.01)	0.5812
	ROW	8626	371 (4.3)	4.6	8585	482 (5.6)	6.1	0.77 (0.67–0.88)	0.0001
PLATO major bleeding	US	682	77 (11.3)	12.2	675	74 (11.0)	11.9	1.05 (0.76–1.45)	0.7572
	ROW	8553	884 (10.3)	11.5	8511	855 (10.1)	11.1	1.04 (0.94–1.14)	0.4696
PLATO non-CABG major bleeding	US	682	29 (4.3)	5.1	675	25 (3.7)	4.3	1.20 (0.70–2.04)	0.5115
	ROW	8553	333 (3.9)	4.4	8511	281 (3.3)	3.7	1.19 (1.01–1.39)	0.0330
PLATO major/minor bleeding	US	682	101 (14.8)	16.4	675	92 (13.6)	15.2	1.11 (0.84–1.48)	0.4599
	ROW	8553	1238 (14.5)	16.1	8511	1123 (13.2)	14.6	1.11 (1.02–1.20)	0.0114

KM indicates Kaplan-Meier estimated event rates at 360 days; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; PLATO, Platelet Inhibition and Patient Outcomes; and CABG, coronary artery bypass graft.

*Excluding silent.

Table 3 shows the pattern of aspirin use by landmark points. Higher doses of aspirin were used at randomization and lower doses thereafter. More US patients were treated with high-dose aspirin after day 2 compared with the ROW patients (61% versus 4%). Table 4 and Figure 5 show the treatment HRs for the primary outcome derived from the landmark analyses. The treatment-region interaction significance level remained <0.05 only for aspirin dose at randomization. For landmark points beyond randomization, once the aspirin dose was considered and the 2-way interactions included, the *P* value for a differential region-by-treatment effect was no longer significant. Compared with clopidogrel, ticagrelor was associated with statistically significantly lower rates of the primary outcome for all landmark periods in the ROW patients receiving low-dose aspirin. Ticagrelor patients treated with high-dose aspirin in the United States and the ROW tended to have worse outcomes compared with clopidogrel patients, although the CIs for the treatment HRs are wide. Models also adjusting for nonaspirin predictors of the primary efficacy outcome produced similar results (data not shown).

Figure 6 shows the adjusted HR for low versus high aspirin dose by landmark dates and randomized treatment. Clopidogrel group outcomes did not vary with aspirin dose at any landmark date; for ticagrelor, low-dose aspirin was associated with better outcome at all landmark dates except randomization.

No treatment-by-region interaction was observed for PLATO major bleeding (unadjusted $P=0.9048$; adjusted $P=0.7798$), and no interaction emerged at any landmark date.

Discussion

Differences in treatment effect across regions of the world have previously been reported.[8] Typically, such differences in outcomes and treatment effects can be explained by differences in patient populations or management strategies but not always.[9] In PLATO, the observed regional effect was substantial (HR, 1.25 in North America, 1.27 in the United States, and 0.84 overall) and carried potential clinical and regulatory implications, should it be true. Thus, after the exclusion of systematic errors or differences in study conduct between regions, it was important to explore whether these findings might be due to chance or could be explained by some baseline or postrandomization factor.

Comprehensive statistical analyses of treatment interactions with baseline and postrandomization factors, including 2 different analytic approaches—one based on Cox analysis and the other based on landmark analyses—independently identified aspirin dose as a potential factor explaining in part the treatment-by-region interaction observed. These analyses also excluded as explanations many investigated prerandomization and postrandomization factors. By both statistical analyses, high-dose aspirin was associated with a higher HR for the primary end point with ticagrelor compared with clopidogrel in both the United States and the ROW. Within the ticagrelor group, the lowest event rates were observed in patients receiving low-dose aspirin and the highest in those receiving high-dose aspirin. In contrast, event rates in clopidogrel-assigned patients were similar to rates with high- or low-dose aspirin. However, despite the large number of different analyses supporting the potential role of aspirin maintenance dose to explain the treatment-by-region interac-

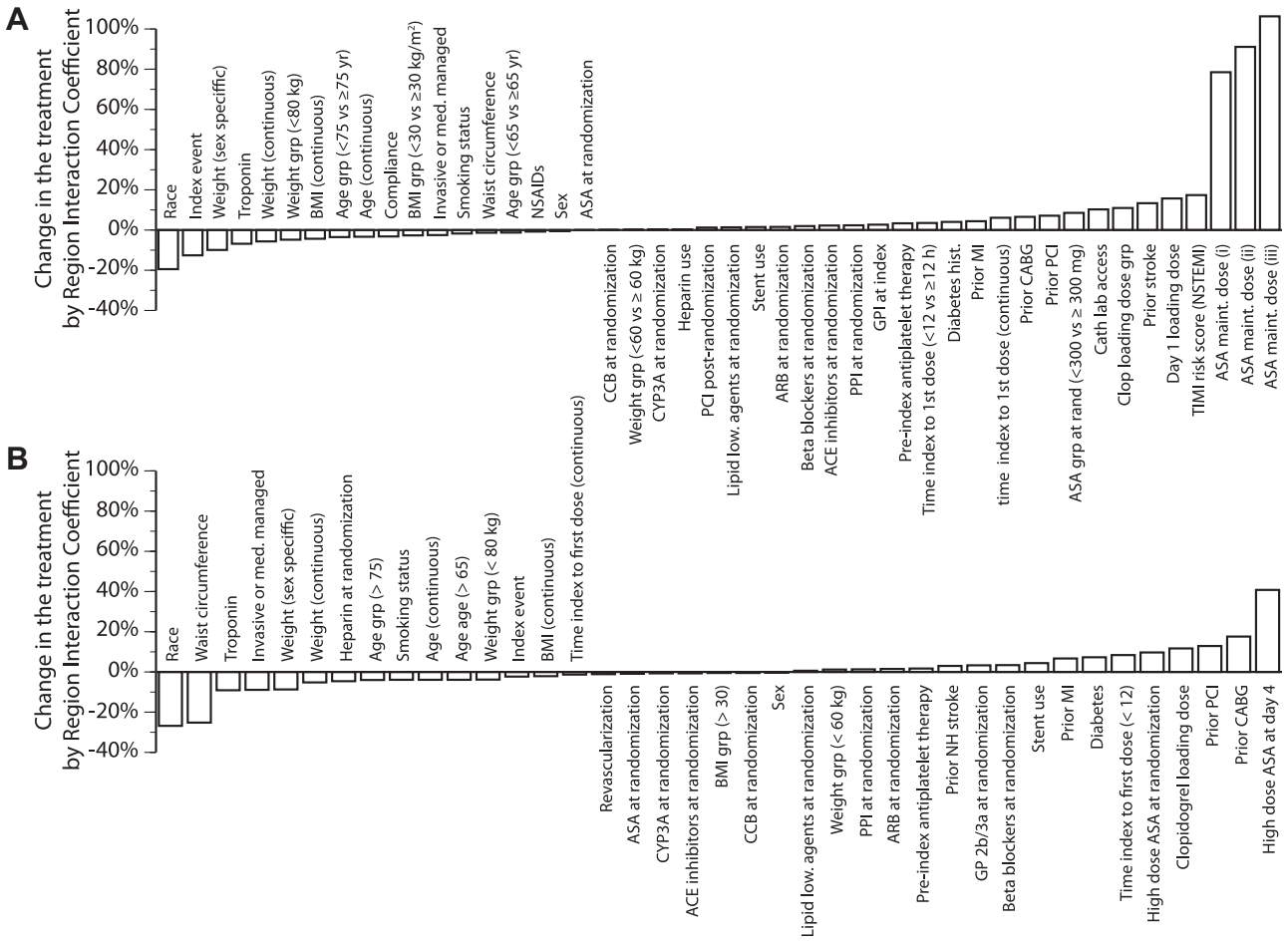

Figure 2. Results of effect modifier analyses (**A**) for the PLATO primary efficacy outcome, expressed as percent decrease in the treatment-region interaction term for each of 46 expressions of 37 factors separately analyzed, and (**B**) for the day 4 landmark analysis of the primary efficacy outcome for each of 39 expressions of 27 variables, including the aspirin dose taken only on day 4. For **A**, aspirin dose definitions are (1) based on all aspirin given between start of study drug and primary event/censoring in patients taking aspirin for at least 5 days; (2) identical to 1 except in all patients taking aspirin at least 2 days; and (3) based on aspirin doses from day 2 to the earliest of cessation of randomized therapy or primary event/censoring. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, aspirin; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; Clop, clopidogrel; GPI, glycoprotein inhibitor; MI, myocardial infarction; NSAIDS, nonsteroidal antiinflammatory drugs; NSTEMI, non–ST-segment–elevation MI; PCI, percutaneous coronary intervention; and PPI, proton pump inhibitor.

tion, statistical evaluations still indicate that the observed regional interaction and pattern of results seen across regions and countries are consistent with what might be expected by chance alone in a large, multiregional clinical trial with multiple exploratory analyses.

Currently, no definitive biological rationale explains why ticagrelor should be less effective than clopidogrel in the presence of a high aspirin maintenance dose. However, there are some potential hypotheses to explain why higher aspirin doses may attenuate the treatment effect of ticagrelor. Aspirin

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100–<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100–<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)

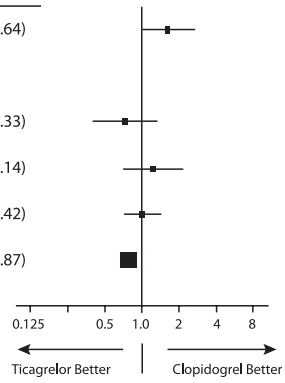

Figure 3. Hazard ratios (HR) and associated 95% confidence intervals (CI) comparing ticagrelor and clopidogrel for the primary efficacy outcome according to region (United States and rest of world [non-US]) and dose category for median maintenance aspirin (ASA) dose. N denotes number of patients; E, number of events. *HR was not calculated owing to small number of events.

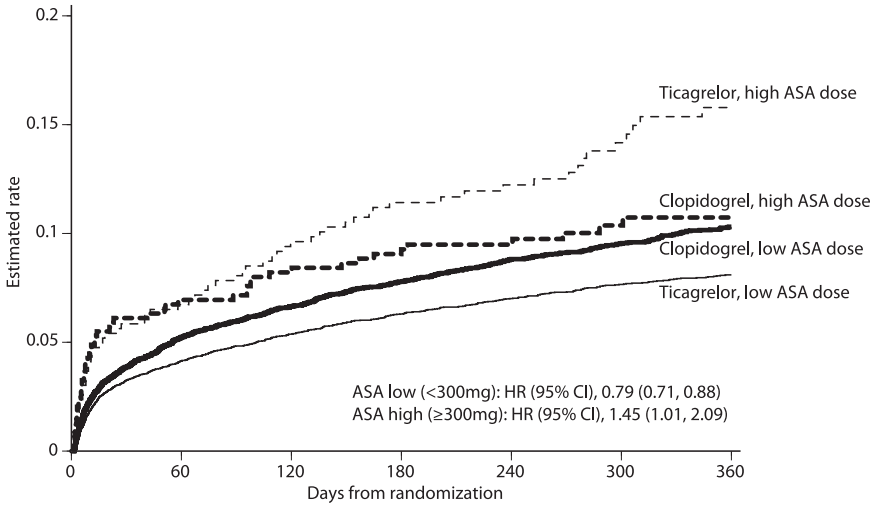

Figure 4. Kaplan-Meier estimated event rates from randomization through 360 days for the primary efficacy outcome by blinded treatment, randomly assigned, and open-label median maintenance aspirin (ASA) dose at investigator discretion. CI indicates confidence interval; HR, hazard ratio.

exerts an antithrombotic effect through inhibition of platelet cyclooxygenase, thus reducing thromboxane A_2 release, but it also inhibits endothelial release of prostacyclin in a dose-dependent fashion at daily doses >80 mg.[10] Prostacyclin reduces platelet reactivity and may contribute synergistically in vivo to the antiplatelet effects of $P2Y_{12}$ inhibitors.[11] Consequently, the therapeutic effects of a higher mean level of $P2Y_{12}$ inhibition, as achieved by ticagrelor in the PLATO study compared with clopidogrel,[12] may be attenuated when endogenous prostacyclin production is inhibited. The effects of aspirin on platelet reactivity are relatively limited compared with $P2Y_{12}$ inhibition.[13] Furthermore, it has been suggested that $P2Y_{12}$ inhibition alone may partially inhibit platelet thromboxane A_2 synthesis,[14,15] and in the presence of strong $P2Y_{12}$ inhibition, the additional effects of higher aspirin doses may result in a reduction of prostacyclin release, potentially shifting the influence of aspirin to a prothrombotic effect.[16] Consistent with the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT/OASIS 7) trial,[17] no association of aspirin maintenance dose with ischemic event rates in the clopidogrel group was observed. Further investigations in vitro and in animals and humans, and preferably prospective randomized, controlled trials, are needed to understand the role of these complex pathobiological interactions. Overall, the absence of a stronger biological rationale suggests that chance alone rather than aspirin dose must remain a potential explanation for the geographic inconsistency in the PLATO results.

The optimal dose of aspirin when used in combination with other platelet inhibitors in the setting of short- and long-term treatment in patients with ACS, with stable coronary artery disease, or after percutaneous coronary intervention is still not clearly defined from large randomized, controlled trials. This explains why previous practice guidelines from the American College of Cardiology/American Heart Association and the European Society of Cardiology differed in their recommendations for aspirin dose in patients with non–ST-segment elevation MI and ST-elevation MI. However, the recently updated American guidelines and the European guidelines recommend low-dose aspirin (75 to 162 mg/d or 75 to 100 mg/d, respectively) for long-term treatment in ACS even after percutaneous coronary intervention with stenting.[4,18,19] The outdated differences in recommendations by the international societies may have contributed to the aspirin dosing regimens seen in the United States compared with the

Table 3. Aspirin Use at Different Landmark Points

	Overall				United States				Rest of the World			
		Aspirin Dose, %				Aspirin Dose, %				Aspirin Dose, %		
Landmark Point	n	0 mg	1–299 mg	≥300 mg	n	0 mg	1–299 mg	≥300 mg	n	0 mg	1–299 mg	≥300 mg
Randomization	18 624	6.4	54.2	39.3	1413	6.3	25.1	68.6	17 211	6.5	56.6	36.9
At day 2	18 217	6.4	85.3	8.3	1375	4.7	34.3	61.0	16 842	6.6	89.5	3.9
At day 4	18 071	6.7	86.2	7.1	1362	4.3	37.7	58.0	16 709	6.9	90.1	2.9
At day 9	17 814	7.0	86.2	6.9	1341	3.7	39.3	57.0	16 473	7.2	90.0	2.8
At day 30	17 441	6.8	86.9	6.3	1311	3.1	42.1	54.8	16 130	7.1	90.5	2.4
At day 60	17 142	6.8	87.8	5.4	1288	3.1	43.8	53.1	15 854	7.1	91.4	1.5
At day 90	16 975	7.0	87.8	5.2	1274	3.9	44.0	52.0	15 701	7.2	91.4	1.4
At day 180	16 258	7.3	88.0	4.7	1222	3.7	48.9	47.4	15 036	7.5	91.2	1.3

Table 4. Hazard Ratios and Kaplan-Meier Estimates at 360 Days by Region and Aspirin Dose: Landmark Analysis

			Low-Dose Aspirin (<300 mg/d)			High-Dose Aspirin (≥300 mg/d)		
Landmark Point	Interaction *P**	Region	Ticagrelor	Clopidogrel	HR (95% CI)	Ticagrelor	Clopidogrel	HR (95% CI)
Randomization	0.0211	US	12.5	13.4	1.16 (0.82–1.64)	12.6	8.6	1.33 (0.96–1.84)
		ROW	9.8	12.6	0.78 (0.69–0.88)	9.2	10.5	0.89 (0.76–1.04)
At day 2	0.2960	US	9.3	10.1	1.00 (0.64–1.56)	10.6	7.1	1.41 (0.94–2.11)
		ROW	8.0	10.1	0.79 (0.71–0.88)	10.1	9.0	1.11 (0.73–1.69)
At day 4	0.3915	US	8.2	9.3	1.00 (0.63–1.95)	10.1	6.5	1.37 (0.89–2.12)
		ROW	7.6	9.5	0.80 (0.72–0.89)	9.7	9.7	1.10 (0.68–1.76)
At day 9	0.3307	US	8.3	7.7	1.02 (0.62–1.67)	8.6	5.6	1.63 (1.02–2.63)
		ROW	6.5	8.4	0.79 (0.70–0.89)	11.7	7.9	1.27 (0.77–2.11)
At day 30	0.1952	US	6.8	6.7	1.11 (0.63–1.95)	8.1	3.7	2.05 (1.17–3.61)
		ROW	5.0	6.7	0.76 (0.66–0.87)	7.5	5.7	1.40 (0.74–2.66)
At day 60	0.5685	US	5.1	6.0	0.94 (0.50–1.78)	8.7	3.0	2.78 (1.48–5.21)
		ROW	4.1	5.4	0.78 (0.67–0.91)	10.4	5.3	2.30 (1.08–4.89)
At day 90	0.3054	US	4.3	5.0	1.09 (0.54–2.20)	8.2	2.7	2.62 (1.35–5.08)
		ROW	3.4	4.6	0.75 (0.63–0.89)	7.7	5.8	1.80 (0.79–4.11)
At day 180	0.9526	US	2.4	3.1	0.75 (0.28–1.99)	5.2	1.7	3.54 (1.28–9.82)
		ROW	1.9	2.7	0.72 (0.57–0.92)	6.4	1.4	3.44 (0.94–12.6)

CI indicates confidence interval; HR indicates hazard ratio; and ROW, rest of the world. The ticagrelor and clopidogrel columns present Kaplan-Meier rates at 360 days.

**P* value is for the treatment-by-region interaction.

ROW. On the basis of the PLATO results, it may well be that there is a further need to reevaluate the optimal aspirin dose in relation to whether it is used alone or in combination with other platelet or coagulation inhibitors.

There are several limitations to these analyses. Despite the large sample size in the PLATO trial, only 1413 patients were enrolled in the United States and only 676 US and 280 ROW patients took ≥300 mg maintenance aspirin. The effect of

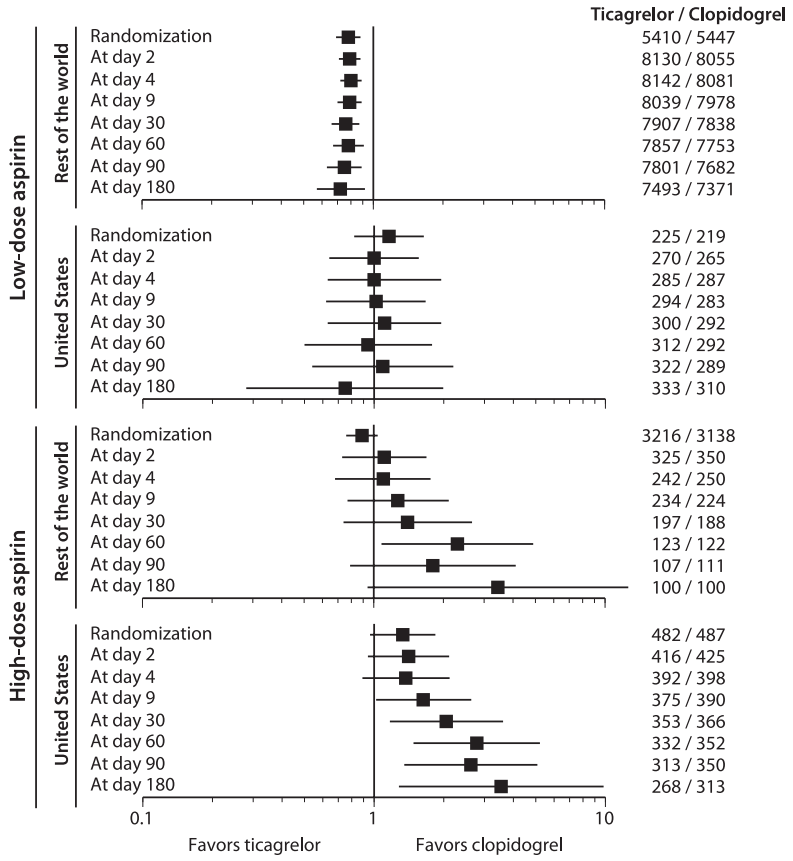

Figure 5. Hazard ratios (■) and associated 95% confidence intervals comparing ticagrelor and clopidogrel for the primary efficacy outcome by the dose of aspirin taken on each of 8 landmark dates (<300 mg=low-dose, ≥300 mg=high-dose) and by region. The rightmost column shows the numbers of patients for ticagrelor and clopidogrel in each analysis.

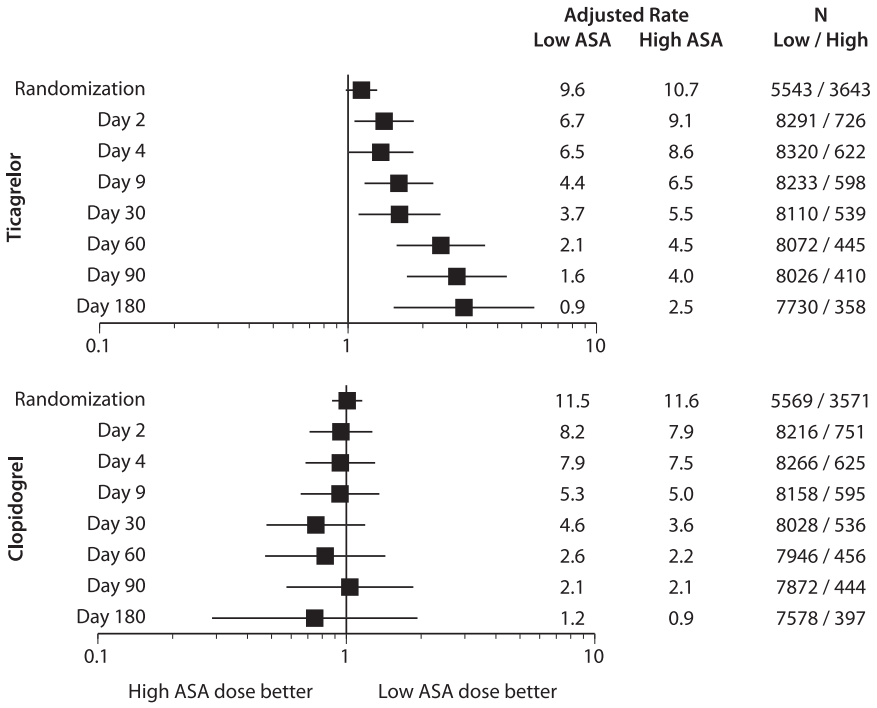

Figure 6. Hazard ratios (■) and associated 95% confidence intervals comparing outcomes for those patients taking <300 mg aspirin (low ASA) and those taking ≥300 mg aspirin (high ASA) on each of 8 landmark dates for the primary efficacy outcome and for each randomized treatment. The rightmost column shows the numbers of patients in the low- and high-dose aspirin groups for each analysis.

treatment assignment across 4 global regions was a prespecified analysis for PLATO, but the analysis for the United States alone was post hoc and data driven. No adjustments were made for multiple comparisons, and the number of preplanned interaction tests serves to increase the likelihood of spurious findings. Subgroup analyses are potentially hazardous even when performed with appropriate thought and rigorous statistical methodology. Subgroups defined by events, procedures, or treatments, including aspirin dosing, that occur or change after randomization require careful consideration because of the potential confounders and biases that may be introduced. Statistical techniques can attempt to adjust only for suspected biases using information collected; unknown factors can easily be contributory.[20] Because of the limitations of these exploratory analyses, the findings that support aspirin dose as a potential explanation should be considered cautiously. The definitive way to evaluate potential role of aspirin dose is by a randomized, clinical trial.

Conclusions

The PLATO trial met its primary end point with a statistically significant overall 16% relative rate reduction in cardiovascular death, MI, or stroke with ticagrelor compared with clopidogrel in patients with ACS. In a prespecified analysis of the treatment effect across regions, the HR favored ticagrelor in the rest of the world but not in North America. In statistical analyses by 2 independent groups, aspirin maintenance dose was identified as a potential explanation of the regional differences, although the play of chance remains another possible explanation. These analyses and current guideline recommendations support that, during potent $P2Y_{12}$ inhibition with ticagrelor in patients with ACS, low-dose maintenance aspirin is likely associated with the most favorable outcomes.

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CLINICAL PERSPECTIVE

In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor prevented the composite of cardiovascular death, myocardial infarction, and stroke better than clopidogrel in a broad acute coronary syndrome population, without increased risk of overall major bleeding. Preplanned analyses examined variation in the treatment effect in relation to 31 demographic and patient characteristics and found a nominally significant interaction of treatment with region. Clopidogrel was associated with a nonsignificant trend of better outcome in North America, whereas ticagrelor was associated with better outcome in the other regions combined. Lower maintenance doses of aspirin were used in the other regions. Of 37 baseline and postrandomization factors explored with Cox regression and separately with landmark techniques, only aspirin dose explained a substantial fraction of the regional interaction; however, given the limitations of these post hoc analyses, the play of chance remains an alternative explanation. Despite robust statistical techniques, a randomized clinical trial is the definitive approach to understanding the dose of aspirin and outcomes with ticagrelor and clopidogrel. Current guidelines for the management of patients with acute coronary syndromes recommend low-dose maintenance aspirin; during potent $P2Y_{12}$ inhibition with ticagrelor in patients with acute coronary syndromes, low-dose maintenance aspirin is associated with favorable outcomes.