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Ticagrelor Effects on Myocardial Infarction and the Impact of Event Adjudication in the PLATO (Platelet Inhibition and Patient Outcomes) Trial

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Objectives This study sought to report the treatment effect of ticagrelor on myocardial infarction (MI) and the strategy for and impact of event adjudication in the PLATO (Platelet Inhibition and Patient Outcomes) trial.

Background In PLATO, ticagrelor reduced cardiovascular death, MI, or stroke in patients with acute coronary syndromes (ACS).

Methods A clinical events committee (CEC) prospectively defined and adjudicated all suspected MI events, on the basis of events reported by investigators and by triggers on biomarkers. Treatment comparisons used CEC-adjudicated data, and per protocol, excluded silent MI.

Results Overall, 1,299 (610 ticagrelor, 689 clopidogrel) MIs reported by the CEC occurred during the trial. Of these, 1,097 (504 ticagrelor, 593 clopidogrel) contributed to the primary composite endpoint. Site investigators reported 1,198 (580 ticagrelor, 618 clopidogrel) MIs. Ticagrelor significantly reduced overall MI rates (12-month CEC-adjudicated Kaplan-Meier rates: 5.8% ticagrelor, 6.9% clopidogrel; hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.75 to 0.95). Nonprocedural MI (HR: 0.86; 95% CI: 0.74 to 1.01) and MI related to percutaneous coronary intervention or stent thrombosis tended to be lower with ticagrelor. MIs related to coronary artery bypass graft surgery were few, but numerical excess was observed in patients assigned ticagrelor. Analyses of overall MIs using investigator-reported data showed similar results but did not reach statistical significance (HR: 0.88; 95% CI: 0.78 to 1.00).

Conclusions In patients with ACS, ticagrelor significantly reduced the incidence of MI compared with clopidogrel, with consistent results across most MI subtypes. CEC procedures identified more MI endpoints compared with site investigators. (A Comparison of Ticagrelor [AZD6140] and Clopidogrel in Patients With Acute Coronary Syndrome [PLATO]; NCT00391872) (J Am Coll Cardiol 2014;63:1493–9) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACS = acute coronary syndrome(s)

CABG = coronary artery bypass graft

CEC = Clinical Events Committee

CI = confidence interval

CK-MB = creatine kinase-MB

HR = hazard ratio

MI = myocardial infarction

NSTEMI = non–ST-segment elevation myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

In the PLATO (Platelet Inhibition and Patient Outcomes) trial (NCT00391872), ticagrelor prevented the composite of cardiovascular death, myocardial infarction (MI), and stroke compared with clopidogrel in a broad acute coronary syndromes (ACS) population (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.77 to 0.92; $p < 0.001$), without increased risk of overall major bleeding, but with a higher rate of bleeding not related to coronary artery bypass grafting (CABG) (1,2). A reduction in MI was observed with ticagrelor (HR: 0.84; 95% CI: 0.75 to 0.95; $p = 0.005$). A clinical events committee (CEC) was used to systematically identify and adjudicate cause of death and all suspected MI and stroke events.

Our objective was to analyze the types of MI events, the timing, and the treatment effects observed, as well as to review the CEC process and describe the concordance between the site investigator-reported MI events and the CEC-adjudicated results.

Methods

The PLATO trial design, patient population, study protocol procedures, outcome definitions, and trial results have been previously published (1,3). The protocol was approved by national and institutional regulatory authorities and ethics committees, and all patients 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/day, 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 stent placement, the protocol allowed 325-mg/day aspirin for ≤6 months (5). Decisions about coronary angiography, revascularization procedures, and pharmacotherapy were left to the discretion of the treating physician.

Events. Patients were followed after discharge from the index hospitalization at 1, 3, 6, 9, and 12 months. Site investigators were to report all suspected cardiac ischemic events and characterize them as ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), unstable angina, stable angina, or other. The last scheduled visit was considered the censoring event, and no endpoint events that occurred after this visit were used in the analysis of the trial.

The CEC developed a comprehensive strategy to identify all suspected deaths, cardiac ischemic events, strokes, and bleeding events. The approach was documented in a separate charter that was prepared by the academic leadership with review and comments by the sponsors and the Executive Committee. This report focused on the cardiac ischemic events and the MI component of the primary endpoint. All suspected MI events were identified by the following mechanisms: 1) the site investigator reported an MI on the

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case report form; 2) cardiac biomarker data provided by the site investigators on the case report form and from central laboratories were evaluated for elevations consistent with an MI or recurrent MI; and 3) a novel method was used to evaluate trends in biomarker data during the index hospitalization to identify potential re-elevation in markers that would suggest a potential MI requiring review by the CEC.

The relatively novel method involved 2 blinded physicians independently reviewing plots of creatine kinase-MB (CK-MB) and troponin values in relation to time of randomization, revascularization procedures, and recurrent ischemic events, with the aim of identifying patients with stable or falling biomarkers before percutaneous coronary intervention (PCI) or CABG and those with post-randomization CK-MB elevations (6). The plots were based on a semi-logarithmic scale that displayed biomarker values in 2 dimensions, with time from randomization (in hours) provided on the X-axis (linear scale) and biomarkers indexed by the upper limit of normal on the Y-axis (logarithmic scale). Each plot was reviewed by 2 physicians (K.W.M., C.H.); if either physician indicated that there was a potential re-elevation in biomarkers suggestive of an endpoint event, the event was sent to the CEC for adjudication. This task was performed by physicians rather than a computer program because of the difficult interpretations posed by the complex relationships between timing of symptoms, procedures, and biomarker release patterns.

All suspected cardiac ischemic events were adjudicated independently by 2 physicians. If the physicians agreed that an event did or did not occur, the event was considered complete. If the physicians disagreed, the event was reviewed by a committee of 3 physicians and a final decision rendered. The CEC personnel and the CEC physician reviewers were blinded to the study drug assignment.

The definitions for MI and the PLATO classification of MI types are listed in Online Appendix A. For each MI event that was adjudicated as meeting endpoint criteria, the physicians recorded type of MI according to the following: nonprocedural, within 24 h after PCI, within 24 h after CABG, MI resulting in death before cardiac markers ascertainment, silent MI, STEMI, NSTEMI, unknown STEMI/NSTEMI, or Q-wave, non–Q-wave, or Q-wave status not evaluable. MI events were categorized post-hoc on the basis of the universal MI definition from 2007 (7) before the revised definition published in 2012 (8) as either: 1) all MIs not associated with PCI, CABG, stent thrombosis, or death; 2) MI associated with death; 3) MI associated with PCI; 4) MI associated with stent thrombosis; or 5) MI associated with CABG.

Statistical analysis. Categorical variables are summarized as frequencies and percentages, and continuous variables as medians and quartiles. HRs comparing randomized treatments (ticagrelor vs. clopidogrel) were derived from Cox proportional hazards models. Competing risk of death was accounted for by censoring patients at time of death.

All exploratory analyses used SAS software (version 9.2, SAS Institute, Cary, North Carolina) and report nominal significance levels without adjustment for multiplicity.

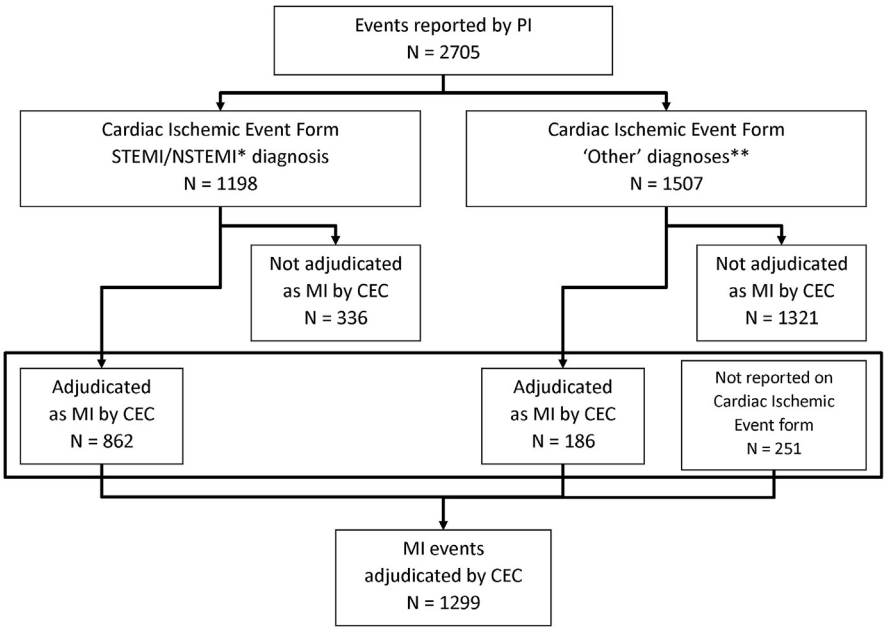

Figure 1 Suspected Events Identified by the Site Investigators and the CEC in PLATO

*Include events with final diagnosis "Other" with text suggesting MI. **Include events with final diagnosis "Unstable Angina", "Stable Angina", and "Other" with text suggesting MI. CEC = clinical events committee; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PI = principal investigator; STEMI = ST-segment elevation myocardial infarction.

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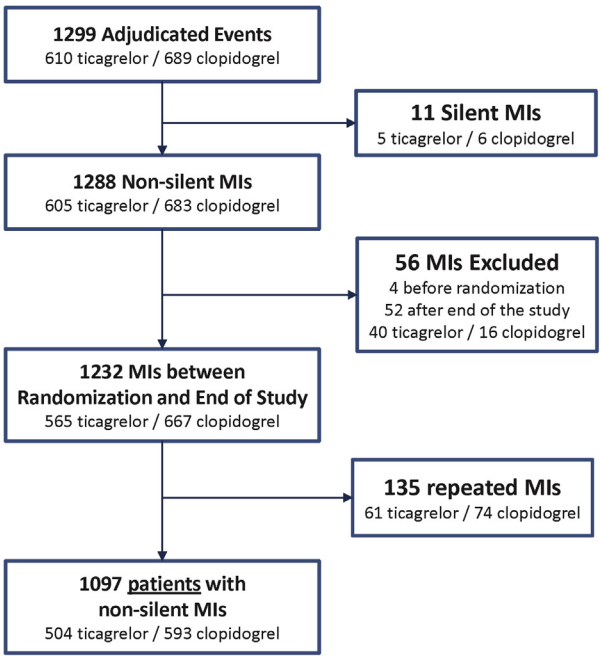

Figure 2 MI Events by Treatment Reported by the CEC

Abbreviations as in Figure 1.

Results

A total of 5,447 events were identified as potential MI events using the comprehensive processes described and processed through the CEC for adjudication. Of the 5,447 events, 2,705 (49.7%) were identified by the site investigator as cardiac ischemic events (Fig. 1): 1,198 (44%) were reported as MI events by the site investigators, and 1,507 (56%) as various cardiovascular events that could potentially have been an MI. The remaining 2,742 (50.3%) of the 5,447 events were identified by other mechanisms, including a computer algorithm, reviews of electrocardiograms, and plot reviews. From these 2,742 events, an additional 251 events not reported by the site investigator were reported by the CEC as MI events.

Overall, of the 5,447 events adjudicated by the CEC, 1,299 MI events were reported to have occurred by the CEC (610 ticagrelor, 689 clopidogrel). Of these 1,299 MI events, 1,288 were nonsilent MIs, and 1,232 were nonsilent MIs between randomization and the end of the study (Fig. 2). Finally, after removing multiple MIs in some patients, a total of 1,097 patients with nonsilent MIs (504 ticagrelor, 593 clopidogrel) were available for analyses of the MI endpoint. Figure 2 shows the reasons why the 202 (1,299 − 1,097) MI events were excluded from the MI analyses for efficacy. For the 52 MIs reported after the end-of-study censoring date occurred, the median (quartiles) for the number of days after censoring was 14 (9, 25): 15 (8, 26) for ticagrelor (n = 37) and 13 (9, 23) for clopidogrel (n = 15).

Table 1 shows the treatment effect by type of MI for the first MI event for each patient reported by the CEC. The most common MI type was nonprocedural. Ticagrelor significantly reduced overall 12-month Kaplan-Meier MI rates (5.8% ticagrelor, 6.9% clopidogrel; HR: 0.84; 95% CI: 0.75 to 0.95; p = 0.005). The direction of the treatment effects was consistent across the MI types except for CABG-related, but there were few of these events, and CIs were wide. Figure 3 shows the Kaplan-Meier curves by MI type and treatment. The treatment effects were observed early and maintained over time. Table 1 also shows the treatment

Table 1 Treatment Effect by Type of MI as Classified by the CEC or Site Investigator

Type of MI	No. of Events*	No. of Events: Ticagrelor	No. of Events: Clopidogrel	HR (95% CI) Ticagrelor vs. Clopidogrel
Classified by CEC†	1,097	504	593	0.84 (0.75–0.95)
STEMI	275	117	158	0.74 (0.58–0.94)
NSTEMI	760	356	404	0.88 (0.76–1.01)
Not evaluable	92	40	52	0.77 (0.51–1.16)
Q-wave	77	37	40	0.92 (0.59–1.44)
Non–Q-wave	708	333	375	0.88 (0.76–1.02)
Q-wave not evaluable	368	160	208	0.76 (0.62–0.94)
Nonprocedure related	652	303	349	0.86 (0.74–1.01)
Procedure-related	304	144	160	0.90 (0.72–1.12)
PCI-related	223	99	124	0.79 (0.61–1.03)
CABG-related	82	45	37	1.21 (0.78–1.87)
Associated with stent thrombosis	172	69	103	0.67 (0.49–0.90)
Classified by site investigator	975	459	516	0.88 (0.78–1.00)
STEMI	352	156	196	0.79 (0.64–0.98)
NSTEMI	594	287	307	0.93 (0.79–1.09)
Other	60	29	31	0.93 (0.56–1.55)

Values are n or hazard ratios (95% CIs). *Number of events of each type. For patients with multiple events of the same type, only the first event is counted. Patients can have events of more than 1 type and be counted in multiple rows. †Excluding silent MIs.

CABG = coronary artery bypass graft; CEC = clinical events committee; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

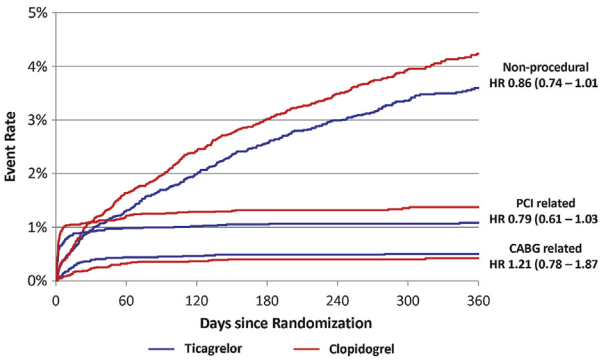

Figure 3 Treatment Effect by Type of MI

CABG = coronary artery bypass graft; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.

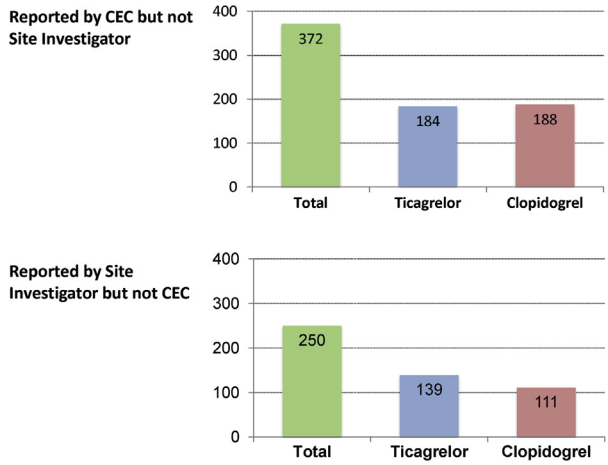

Figure 5 Disagreements Between CEC and Site Investigators

Abbreviations as in Figure 1.

effect for MIs defined by the presence or absence of ST-segment elevation or Q-waves as reported by the CEC.

Site investigators reported a total of 1,198 MIs (580 ticagrelor, 618 clopidogrel) with 1,128 of them between randomization and end of the study. Overall, there were more CEC-adjudicated MIs (1,299) than site investigator-reported MIs (1,198). Figure 4 shows the proportion of CEC-adjudicated MIs and site investigator-reported MIs that were nonprocedural, PCI-related, or CABG-related. Table 1 shows the treatment effect by type of MI reported by the site investigator. The treatment effects with ticagrelor compared with clopidogrel were consistent compared with the same classifications reported by the CEC, although for total MIs, the 95% CI crossed 1.0.

Concordance between the CEC and site investigators was explored at the patient level. In this analysis, patients were classified as having or not having an MI between randomization and the end of the study on the basis of the CEC and site investigator information. Overall, the CEC and the site investigators agreed that 17,277 patients did not have an MI event, and that 725 patients had an MI event, for a 96.7% agreement (Table 2). Of the patients with an MI determined by the CEC (n = 1,097), the site investigators reported that an MI occurred for 725 (66.1%). For those patients for whom the site investigator reported an MI, the CEC confirmed an MI for 74.4%. Overall, the CEC identified 184 MIs in the ticagrelor patients and 188 MIs in the clopidogrel patients not reported by the site investigators (Fig. 5). Likewise, for events reported by the site investigators that were not confirmed to meet study criteria for an MI by the CEC, there

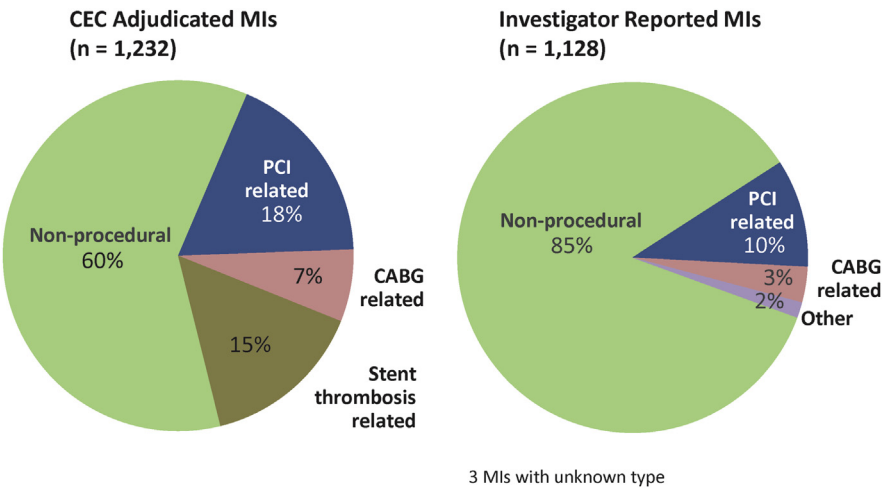

Figure 4 Breakdown of CEC-Adjudicated MIs and Site Investigator-Reported MIs

Abbreviations as in Figures 1 and 3.

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Table 2 Comparisons: CEC and Site Investigator

	CEC		
Investigator Reported	Yes	No	Total
Yes	725	250	975
No	372	17,277	17,649
Total	1,097	17,527	18,624

Values are n. Using the first event for patients with multiple events reported or adjudicated.
Abbreviation as in Table 1.

were 139 MIs in the ticagrelor arm and 111 MIs in the clopidogrel arm. Table 3 shows the MI types.

A total of 2,626 plots were generated, and 2,622 with sufficient data were processed and reviewed by 2 physicians as planned. Of the 2,622, 284 (10.8%) were identified by at least 1 of the 2 physicians as requiring adjudication by the CEC. Of the 284 that went to formal adjudication, the CEC called 59 (20.8%) an MI and 225 (79.2%) not an MI. Of those called an MI, 26 were in the ticagrelor arm and 31 were in the clopidogrel arm (HR: 0.92; 95% CI: 0.55 to 1.54).

Discussion

In the PLATO trial, ticagrelor significantly reduced the risk of subsequent MI (1). These analyses show a consistency of this treatment benefit in reducing each of the different MI types, including nonprocedural (e.g., spontaneous) and PCI-related MI events, and those defined by more traditional methods, such as presence or absence of Q-waves or ST-segment elevation. In addition, site investigators reported fewer MI events compared with the CEC, but analyses of treatment effects using site investigator-reported or CEC-reported MIs were similar; however, with more events, the findings were more statistically robust with the CEC data.

Recurrent MI following ACS remains a common event despite improvement in therapies in the past decade. In PLATO, 1,299 MI events occurred during a median of 9 months of follow-up with continued accrual over time. The use of continuous dual antiplatelet therapy with ticagrelor and aspirin showed robust effects early with evidence of continued accrual of benefit over time. Significant reduction in nonprocedural endpoint MIs was observed. The PCI-related MIs occurred early, with a reduction in the hazard of MI with ticagrelor similar to the overall MI hazard reduction (0.794 vs. 0.840). The number of CABG MIs was small (45 ticagrelor, 37 clopidogrel), with a higher number seen with ticagrelor compared with clopidogrel, but with a broad CI.

Site investigators reported fewer MIs than the CEC. This is consistent with previous experiences (9,10). In PLATO, the treatment benefit observed with ticagrelor compared with clopidogrel on MI was similar using the site investigator-reported or the CEC-reported MI events. Some previous trials have reported differences in trial outcomes when using the CEC-reported events compared with the site investigator-reported events (11), and the reasons are not clear. In PLATO, the proportion of MIs reported by the site investigators as nonprocedural was higher than the proportion reported by the CEC. This is consistent with previous findings and reflects an underreporting of these events likely due to a reluctance to report events that occur from a procedure being performed, or in some situations, a lack of agreement with the definition used or lack of awareness. The novel approach to review plots of cardiac biomarker information integrated with the clinical details identified 54 MIs not reported by the site investigators. This was an efficient strategy to identify early events in patients who predominantly had elevated biomarkers and earlier procedures. A similar approach has been used successfully in other programs by the same CEC group (6).

Table 3 Description of CEC-Adjudicated MIs

	All CEC-Adjudicated MIs (n = 1,299)		
	Reported by PI on CIE Form as STEMI/NSTEMI (n = 862)	Reported by PI on CIE Form But Not as STEMI/NSTEMI (n = 186)	Not Reported by PI on CIE Form (n = 251)
Final diagnosis by PI			
STEMI	285 (33%)	—	—
NSTEMI	554 (64%)	—	—
Unstable angina	—	122 (66%)	—
Stable angina	—	7 (4%)	—
Other	23 (3%)	56 (30%)	—
Missing	—	1 (< 1%)	—
Final diagnosis by CEC			
STEMI	266 (31%)	27 (15%)	11 (4%)
NSTEMI	549 (64%)	138 (74%)	198 (79%)
Not evaluable	47 (5%)	21 (11%)	42 (17%)
Q-wave	66 (8%)	8 (4%)	20 (8%)
Non–Q-wave	500 (58%)	100 (54%)	193 (77%)
Q-wave not evaluable	296 (34%)	78 (42%)	38 (15%)

Values are n (%).
CIE = cardiac ischemic events; PI = principal investigator; other abbreviations as in Tables 1 and 2.

The recently revised universal MI definition (8) has increased the threshold to diagnose a procedural MI by increasing the CK-MB or troponin elevations that must be obtained, but also includes additional criteria, such as ischemic symptoms and angiographic imaging, or electrocardiographic evidence of complications or infarction. We did not collect these data in PLATO and, thus, could not perform additional analyses on MI outcomes and treatment effects using the revised universal definitions.

A recent report (12) using data published in the literature or reported by the Food and Drug Administration in public documents (13) was critical of the CEC processes used in PLATO and other trials. The investigators insinuated impropriety in trial conduct because they concluded from the available data that adjudicated events were added only to the clopidogrel arm by the CEC. Our analyses, performed using the raw data sets, clearly show the flaw in the methodology used by these investigators. Events were identified by the CEC in both study arms that were not reported by the site investigator, and the CEC did not agree with all site investigator assessments on events in both study arms.

Study limitations. The trial was not powered to detect treatment differences in the subtypes of MI using various common reporting categories. We did not collect the MI classification by the site investigator using the universal MI definition, but used the commonly used STEMI and NSTEMI categorizations. Work such as the Food and Drug Administration Standardized Data Collection for Cardiovascular Trials Initiative is a step in the right direction to standardize systematic defining and reporting of MI endpoints (14). Finally, we were unable to fully characterize the reasons for disagreement between the CEC and site investigators, which limited our ability to understand and recommend how sites should report events for future trials.

Conclusions

In patients with ACS, ticagrelor significantly reduced MI compared with clopidogrel, with consistent results across most MI subtypes. CEC procedures identified more MI endpoints compared with site investigators. Understanding CEC processes and concordance between the site investigator and CEC are important to fully interpret trial results.

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Key Words: acute coronary syndrome(s) ■ adjudication ■ clinical events committee ■ clopidogrel ■ myocardial infarction ■ outcomes ■ ticagrelor.

APPENDIX

For supplemental material regarding the definitions for MI and the PLATO classification of MI types, please see the online version of this article.