CLINICAL RESEARCH STUDY

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Impact of Bleeding on Myocardial Infarction, Stroke, and Death During 12 Months Dual Antiplatelet Therapy After Acute Coronary Syndrome

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ABSTRACT

BACKGROUND: Bleeding remains a complication during dual antiplatelet therapy (DAPT) for acute coronary syndrome (ACS). Some data suggest a link between bleeding and worsened vascular outcomes. However, this association is unclear, due to omitting of minor bleedings when applying conservative scales. In contrast, the Platelet Inhibition and Outcomes (PLATO) trial classification used broad realistic capturing of all bleedings.

METHODS: Access was gained to the Food and Drug Administration-issued adjudication data set on which post hoc analyses of bleeding, myocardial infarction (MI), stroke, and death were conducted. Bleeding was defined as minimal, minor, major, and life-threatening or fatal (LTOF) as per the original PLATO scale.

RESULTS: Among 18,624 enrollees, 10,705 adjudicated events occurred across 7171 patients. There were 618 minimal, 1412 minor, 1216 major, and 536 LTOF bleedings for the total of 3782 events reported in 3387 patients. There were 938 deaths, 2751 MIs and 359 strokes. The overall bleeding was 20.3%, exhibited in 19.2% patients. Total bleeds were associated with less deaths (odds ratio [OR]: 0.55, 95% confidence interval [CI]: 0.47-0.63) and MI (OR: 0.47, 95% CI: 0.41-0.54; $P < .001$ for both). There were no differences in deaths (OR: 1.11, 95% CI: 0.93-1.34; $P = .24$), but less MIs (OR: 0.72. 95% CI: 0.59-0.86; $P < .001$), and more strokes (OR: 2.17, 95% CI: 1.64-2.88; $P < .001$) after LTOF. Major, minor, and minimal bleeds were associated with less deaths and MI but not strokes.

CONCLUSION: These large uniformly adjudicated data reveal that within 12 months of dual antiplatelet therapy, 1 out of 5 patients experiences bleeding. Overall, bleeding was associated with diminished incidence of death and MI but not strokes.

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KEYWORDS: Antiplatelet therapy; Bleeding; Death; Myocardial infarction; Risks; Stroke

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Conflicts of Interest: VLS reports research grants from the manufacturers of clopidogrel and prasugrel, lecture fees from the clopidogrel manufacturer, consultancy fees from the clopidogrel and ticagrelor manufacturers, and patent fees from Lilly and Boehringer-Ingelheim. DA reports personal fees from Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, MSD, Novartis, Pfizer, Roche Diagnostics, Sanofi and Vifor, as well as research grants to the institution from Medtronic, BMS and Roche diagnostics. J-FT, WK, EH, MHK report none.

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INTRODUCTION

One of the largest controversies of modern antithrombotic strategies is the uncertain relation among the potency and duration of dual antiplatelet therapy (DAPT) with associated bleeding rates,[1-3] and whether bleeding impacts mortality, myocardial infarction (MI), and stroke risks.[4-6] Some data from clinical trials[1-5] and registries[7,8] suggest that such a link is valid; however, this association is not established partly due to capturing of exclusively major or catastrophic events while omitting minor and minimal episodes, and applying restrictive bleeding scales.[9] Although there is some randomized evidence linking improved vascular outcomes and aggressiveness of DAPT, reliable large and uniformly collected data on bleeding event rates are scarce. For example, some evidence from more than 2 decades ago suggested excess mortality[10] and unacceptable bleeding rates[11] with oral glycoprotein IIb/IIIa inhibitors, a fact that discouraged chronic use of these agents beyond the scope of in-hospital interventions. Hence, it is still of interest to assess bleeding events during a period of 12 months of DAPT. One reason for this interest is the fact that, historically, many indication-seeking large-scale clinical trials reported only major or life-threatening bleeding events. However, the Platelet Inhibition and Outcomes (PLATO) study was different. Considering ticagrelor being a reversible agent, the trial used a much broader bleeding classification, collecting and centrally adjudicating all clinically relevant hemorrhages.[12] The hypothesis was that ticagrelor may cause less bleeding than the irreversible comparator clopidogrel, particularly in the most high-risk (eg, ST-elevation myocardial infarction [STEMI] or coronary artery bypass graft [CABG]) subpopulations of the study. Therefore, a realistic bleeding classification has been implemented in PLATO, and bleeding deaths were included in the trial primary endpoint.[12,13] Despite the fact that this hypothesis failed (ie, ticagrelor did not cause less bleeds than clopidogrel),[13] we now have a rare opportunity to adequately assess bleeding and establish whether and how these hemorrhagic complications are associated with hard end points. We gained access to the Food and Drug Administration (FDA)-issued uniformly adjudicated PLATO event data set, calculated the annual bleeding rates, and correlated them with myocardial infarction (MI), stroke, and death in patients with acute coronary syndrome (ACS) treated with clopidogrel or ticagrelor on top of aspirin.

CLINICAL SIGNIFICANCE

- The overall annual bleeding rate for dual antiplatelet therapy is an alarming 20.3%, exhibited in 19.2% patients with acute coronary syndrome.
- Total bleeds were associated with almost twice fewer deaths and myocardial infarctions, whereas stroke risks were identical.
- There was no statistical correlation between bleeding severity and outcomes or differences between ticagrelor and clopidogrel.

METHODS

Data retrieval: Based on the Freedom of Information Act, we filed a legal complaint in a US federal court (case 1: 21-CV 01572 BAH), reached a joint status report order with FDA and Department of Justice, and received the complete PLATO adjudicated event data set submitted to the FDA by the ticagrelor NDA 22-433 sponsor. (See Figure 1 for details.)

Patients: The detailed description is provided elsewhere.[12,13] Briefly, patients were eligible for enrollment if hospitalized for an ACS with an onset of symptoms during the previous 24 hours. Major exclusion criteria were any contraindication against the use of clopidogrel, fibrinolytic therapy within 24 hours before randomization, a need for oral anticoagulation, an increased risk of bradycardia, and concomitant therapy with a strong cytochrome P-450 3A inhibitor or inducer. Among 18,624 patients enrolled 25% were diabetics, more than 60% received stents, 10% underwent CABG and 46% were treated with prehospital clopidogrel. About 23% of patients discontinued the study drug prematurely. The follow-up duration was restricted to 365 days.

Bleeding: Most bleeding events (except some minimal) were adjudicated according to the PLATO definitions (see Table 1 for details). Each bleeding was characterized by adjudication codes: 6 - minimal; 7 - minor; 8 - major and 9 - life-threatening/or fatal (LTOF) bleeding. The Independent Central Adjudication Committee (ICAC) also evaluated the clinical study data of every patient who underwent CABG during the study to adjudicate for a possible bleeding event, whether or not the investigator designated an event. The ICAC evaluated all bleeding events designated by investigators as LTOF, Major, or Minor; reviewed the information provided by investigators; and applied consistent criteria to categorize each event. Non-CABG bleeding events reported by investigators as minimal were often not adjudicated by the ICAC but were combined for analysis with events adjudicated by ICAC to be minimal. The ICAC determined that some events reported by investigators did not qualify as bleeding events. On occasion, the ICAC identified additional events and directed the sponsor to query a site to register the event for official adjudication. If the investigator agreed, the event was registered and processed by the ICAC.

Statistical Methods: Categorical data were analyzed using frequency and percentage statistics. χ^2 analysis was performed to test for associations between different bleeding types (major: life-threatening/fatal; major: other; minor; minimal; any type of bleed) and end point events (death, MI, and stroke). Unadjusted odds ratios (OR) with 95% confidence intervals (CIs) were reported and interpreted for all χ^2 analyses. All analyses were performed using SPSS Version 28 (IBM Corp.), with the exception of the forest

plot, which was constructed in GraphPad Prism Version 8.0.0 (GraphPad Software). Statistical significance was assumed at a 2-sided alpha value of 0.05.

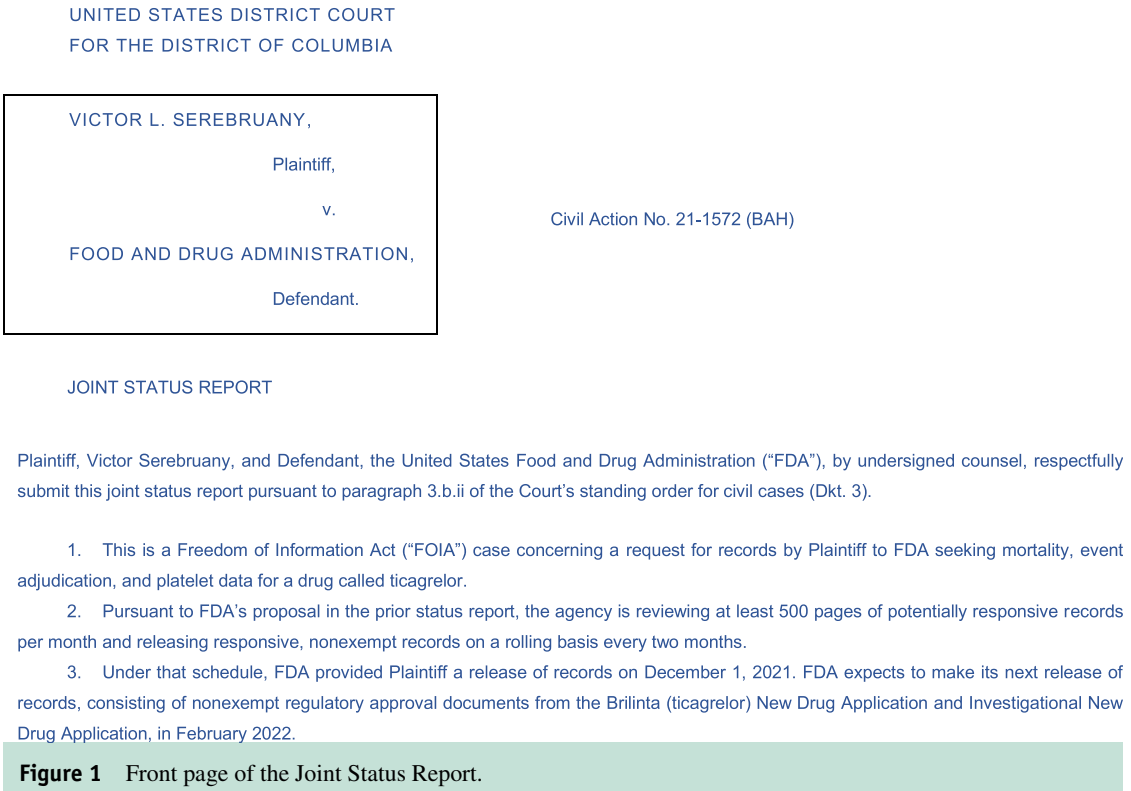
RESULTS

Among 18,624 trial enrollees, 10,705 annual adjudicated events occurred across 7171 patients. There were 618 minimal, 1412 minor, 1216 major, and 536 LTOF for the total of 3782 bleeding events reported in 3387 patients. Single bleeding events occurred in 2597 patients, double in 679, triple in 97, and finally quadruple bleeds were reported in 14 DAPT patients. There were 938 deaths, 751 MIs, and 359 strokes. The flowchart of adjudicated events in PLATO is presented in Figure 2.

The overall annual bleeding event rate for DAPT was 20.3% exhibited in 19.2% patients. Table 2 depicts the associations between bleeding events (stratified according to the severity of the events) and death, MI, and stroke. There was no effect of LTOF on death ($P = .24$), while those events were linked to less MI ($P < .001$) and more strokes ($P < .001$). Those with major, minor, and minimal bleeds had a consistently lower rate of death and MI ($P < .001$ for both) and no significant association to strokes. Likewise, those with a minimal bleed had a lower rate of death ($P < .001$), MI ($P = .003$), but no difference for stroke. Finally, total bleeds were associated with highly significantly less deaths ($P < .001$) and MI ($P < .001$), while stroke risks were identical ($P = .99$) between the bleeding and nonbleeding post-ACS adjudicated cohorts. Finally, these relationships are also depicted in Figure 3, visualized as Forrest plot.

DISCUSSION

There are two main findings of these analyses of a large data set. First, about 1 out of 5 post-ACS patients on DAPT experience clinically relevant (at least minimal) bleeding events over a 12-months therapy duration. The annual bleeding event rate for DAPT with clopidogrel or ticagrelor was 20.3%, and was exhibited in 19.2% patients because some patients experienced several bleedings. Since bleeding in PLATO was captured broadly and adjudicated uniformly, these rates exceed former evidence yielded from various trials[1-5] as well as prescription inserts for ticagrelor[14] and clopidogrel.[15] Second, in contrast to oral GPIIb/IIIa inhibitors, a regimen of 1 year of DAPT appears to be associated with reduced MI and death risks, with less impact on stroke. Surprisingly, LTOF only trended to be associated with more deaths, significantly over twice more strokes, but less MI. The association between LTOF hemorrhages and stroke risks was the only significant although *expected* link between bleeding and excess hard adverse vascular outcomes. All the other associations point to the contrary direction: Patients with major, minor, and minimal bleeds had a consistently lower rate of death and MI and no significant difference in strokes (albeit a trend to less



UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

VICTOR L. SEREBRUANY,
Plaintiff,
v.
FOOD AND DRUG ADMINISTRATION,
Defendant.

Civil Action No. 21-1572 (BAH)

JOINT STATUS REPORT

Plaintiff, Victor Serebruany, and Defendant, the United States Food and Drug Administration ("FDA"), by undersigned counsel, respectfully submit this joint status report pursuant to paragraph 3.b.ii of the Court's standing order for civil cases (Dkt. 3).

1. This is a Freedom of Information Act ("FOIA") case concerning a request for records by Plaintiff to FDA seeking mortality, event adjudication, and platelet data for a drug called ticagrelor.

2. Pursuant to FDA's proposal in the prior status report, the agency is reviewing at least 500 pages of potentially responsive records per month and releasing responsive, nonexempt records on a rolling basis every two months.

3. Under that schedule, FDA provided Plaintiff a release of records on December 1, 2021. FDA expects to make its next release of records, consisting of nonexempt regulatory approval documents from the Brilinta (ticagrelor) New Drug Application and Investigational New Drug Application, in February 2022.

Figure 1 Front page of the Joint Status Report.

Table 1 Definition of Bleeding Events in PLATO

Bleeding Classification in the PLATO trial	
Severity	Criteria
Minimal	Bruising, bleeding gums, oozing from injection sites, and so on not requiring immediate intervention or treatment.
Minor	Requires medical intervention to stop or treat bleeding (eg, epistaxis requiring visit to medical facility for packing).
Major	Any of the following: • Significantly disabling (eg, intraocular with permanent vision loss); • Clinically overt or apparent bleeding associated with a decrease in Hb of 30 g/Lm (1.9 mmol/L; 0.465 mmol/L) to 50 g/L (3.1 mmol/L; 0.775 mmol/L); • Transfusion of 2-3 units (whole blood or packed red blood cells) after bleeding.
Life- threatening/fatal	Any of the following: • Fatal; • Intracranial; • Intrapericardial bleed with cardiac tamponade; • Hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery • Clinically overt or apparent bleeding associated with a decrease in Hb of more than 50g/L (3.1 mmol/L; 0.775 mmol/L); • Transfusion of 4 or more units (whole blood or packed red blood cells for bleeding).

PLATO = Platelet Inhibition and Outcomes.

strokes). Those patients even with minimal bleeds had a lower rate of death and MI with no difference in strokes.

The initial hypothesis of this study was to confirm potential association of properly, broadly, and fairly reported bleeding events with vascular thrombotic outcomes. We expected different results because published, although smaller evidence suggests direct positive link for more bleeding and excess mortality. However, the opposite was true. Based on the index findings, it seems bleeding somewhat indicates the benefit of "excellence" for antiplatelet therapy, resulting in less vascular end points. In fact, should we count only LTOF catastrophic events, then the conclusions will be much less obvious. Not surprisingly the bleeding rates in the index study were much higher than those reported in other major clinical trials[1-5] and registries[7,8] because PLATO deliberately did not limit itself to capturing frequent in-hospital events but expanded to a careful and broad monitoring, reporting and adjudication of delayed bleeds of all severities.[12,13] In fact, the here reported bleeding rates are somewhat underestimated because many minimal events were, after all, not adjudicated, and trial investigators were mostly (except in Sweden and the UK) unfamiliar with the novel bleeding PLATO scale. It is unlikely that PLATO captured all minimal bleeding episodes because the reported low numbers make little sense. When the quantity for minimal bleeds matches with LOFT rates but is twice less than strictly adjudicated minor or major bleeds, the underreporting of minimal events appears obvious. Importantly, the PLATO scale minimal events were not that minimal because superficial sporadic episodes such as petechia and ecchymosis after tooth brushing or shaving are well-established consequences of platelet inhibition but were not counted as minimal and constituted a clear "no event."[13]

One of the main reasons why a realistic bleeding risk assessment and its impact on vascular outcomes still remains unclear is a difficulty to apply the appropriate type of classifications to categorize bleeding.[9] Both conventional thrombolysis in myocardial infarction (TIMI)[16] and Global Use of Strategies To Open (GUSTO)[17] bleeding scales emerged during the era of thrombolytic agent development, when intracranial hemorrhages were the most common life-threatening complications of drug-induced fibrinolysis. Therefore, both classifications may not be well-suited to assess minor bleeding episodes. Among the classifications, TIMI represented the most conservative scale, GUSTO captured additional bleeding events, whereas BleedScore[9,18] and the subsequent Bleeding Academic Research Consortium (BARC) score[19] are the broadest classifications.

The data presented here contradict multiple smaller studies with regard to an association between bleeding and death. The reasons for this disagreement are uncertain but likely linked to the method bleeding was captured, follow-up duration, or the emerging impact of DAPT on adherence.[20] The current investigation confirms that over the 1-year course of DAPT, some patients experience multiple bleeding complications rather than a single event. Several bleeds (mostly dual, but no more than 4) in PLATO were reported in 790 (23.4%) patients. Based on these data, it is conceivable that patients usually tolerate no more than 2-3 such hemorrhagic episodes before therapy discontinuation. These data may be critical for an early identification of patients at high-risk for bleeding and the potential inherent risk of withdrawal from antiplatelet agents.[21] Indeed, should a patient exhibit a first superficial bleeding episode, it is likely that such complications will be repeated during the course of DAPT in about a quarter of patients. Hence, dose reductions or alternative shorter regimens may be required in this particular cohort. Officially, DAPT adherence in PLATO was 82.8%,[12] but the FDA-calculated compliance was 77% with 14% of patients having incomplete follow-up.[20] What have happened with these particular patients is indeed an important piece of missing information for all trials, including PLATO. Moreover, studies with shorter DAPT duration have shown comparable outcomes with longer DAPT durations. If patients with bleeding in

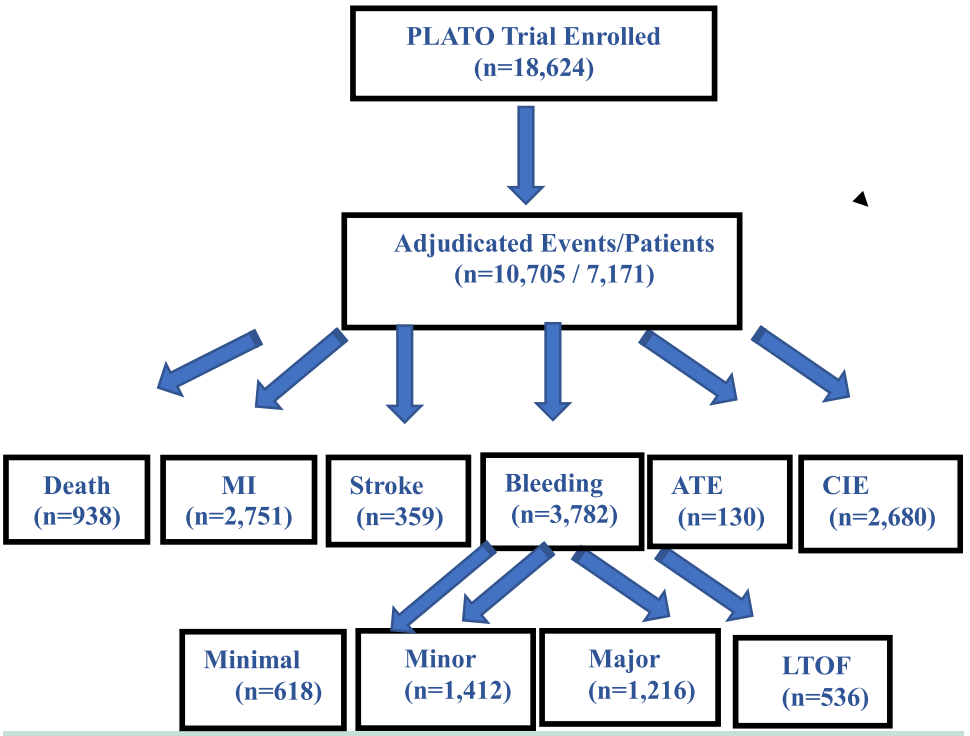


Figure 2 Flowchart of PLATO events reported to the Food and Drug Administration. ATE = aortic thromboembolism; CIE = cerebral ischemic event; LTOF = life-threatening or fatal; MI = myocardial infarc; PLATO = Platelet Inhibition and Outcomes.

the current data set had their P2Y12 inhibitor stopped, further reduction in bleeding would actually help improve outcomes and may reasonably explain our findings.

We deliberately did not triage the outcome of the ticagrelor arm versus the clopidogrel arm for 2 reasons. Since bleeding adjudication was unbiased with similar degree of event adjudication disagreements, the data (not shown) suggest that ticagrelor caused slightly more minor and minimal bleeds than clopidogrel, while LTOF bleeding events were identical. Also, since clopidogrel and ticagrelor constitute more than 90% of currently used DAPT regimen worldwide, the overall pattern seems more important than drug-specific effects. Finally, we applied an all-in approach for this analysis counting all-cause deaths, all MI including type 2, and the stroke + transient ischemic attack (TIA) combination. Importantly, bleeding was adjudicated

Table 2 Association of Different Bleedings with Hard Endpoint Events Among 7171* ACS Patients

Event	Bleed Type	Absent (n, %)	Present (n, %)	*P* Value	OR (95% CI)
Death	LTOF	773 (12.9%)	165 (14.1%)	.24	1.11 (0.93-1.34)
MI	LTOF	1001 (16.7%)	146 (12.5%)	<.001	0.72 (0.59-0.86)
Stroke	LTOF	174 (2.9%)	71 (6.1%)	<.001	2.17 (1.64-2.88)
Death	Major	840 (13.9%)	98 (8.8%)	<.001	0.60 (0.48-0.74)
MI	Major	1016 (16.8%)	131 (11.7%)	<.001	0.66 (0.54-0.80)
Stroke	Major	217 (3.6%)	28 (2.5%)	.07	0.69 (0.46-1.03)
Death	Minor	872 (13.9%)	66 (7.5%)	<.001	0.50 (0.39-0.65)
MI	Minor	1066 (16.9%)	81 (9.2%)	<.001	0.50 (0.39-0.63)
Stroke	Minor	223 (3.5%)	22 (2.5%)	.11	0.70 (0.45-1.09)
Death	Minimal	923 (13.4%)	15 (5.5%)	<.001	0.38 (0.22-0.63)
MI	Minimal	1121 (16.3%)	26 (9.5%)	.003	0.54 (0.36-0.81)
Stroke	Minimal	240 (3.5%)	5 (1.8%)	.14	0.52 (0.21-1.26)
Death	All bleeds	641 (16.0%)	297 (9.4%)	<.001	0.55 (0.47-0.63)
MI	All bleeds	810 (20.2%)	337 (10.7%)	<.001	0.47 (0.41-0.54)
Stroke	All bleeds	137 (3.4%)	108 (3.4%)	.99	1.00 (0.78-1.30)

*Same patient may experience different and/or multiple events. ACS = acute coronary syndrome; Death = all cause; LTOF = life-threatening or fatal; MI = myocardial infarction—all including triggered, excluding silent; OR = unadjusted odds ratio; Stroke = all strokes and TIAs; TIA = transient ischemic attack; 95% CI = 95% confidence interval.

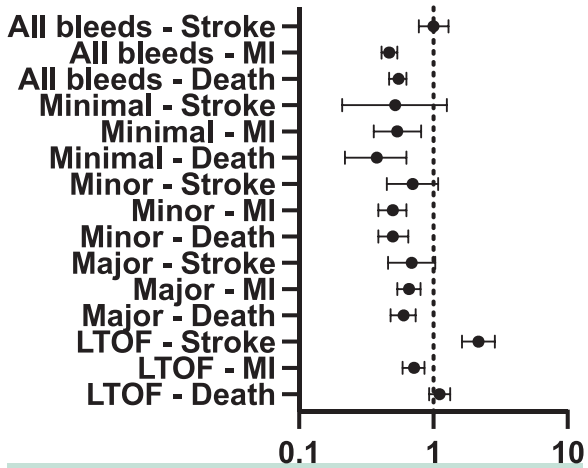


Figure 3 Forest plot of various bleeds and events in the PLATO trial. LTOF = life-threatening or fatal; MI = myocardial infarcation; PLATO = Platelet Inhibition and Outcomes.

methodically, differences in ticagrelor and clopidogrel affiliated rates were clearly identified, and rare autopsy findings or uncommon brain imaging results after strokes in PLATO were all taken into consideration. The association of bleeding with less death and less MI appears as a novelty of the current study; however, the mechanisms of these associations are unclear and deserve further scrutiny. As a hypothesis, chronic DAPT may be excessive in some patients causing less thrombophilia. There might be an (acquired) coagulopathy in some patients beyond diminished platelet inhibition resulting not only in bleeding but also potentially contributing to the decreased risks of thrombotic vascular occlusions.

Strengths and Limitations

There are few strengths worth mentioning: This analysis was conducted within the framework of a governmental database that entailed mandatory event reporting. Independent specialists with an expertise on outcome data mining were used to avoid any potential bias. Solid statistical methods were applied. The sample size for all events represents one of the largest databases, allowing us to make reasonable assessments of event rates and associations. In fact, we analyzed more events than the numbers of enrolled patients in many small trials addressing this topic. There are also several limitations of this study. First, we present post hoc (ie, not prespecified analyses), so the index event data were not collected in a prospective fashion. Second, compliance was not uniformly confirmed by serial detection of clopidogrel and ticagrelor metabolites in all patients. Third, there are no prasugrel data in the PLATO database, which might have been an asset to better understand the risks and advantages of DAPT across the most used antiplatelet drugs. Fourth, these data are somewhat old and perhaps of less relevance to contemporary practice. Clinical practice appears to be more toward shorter periods of DAPT and increasingly toward single antiplatelet agents (at least after 1 month). Fifth, as in any mega indication-seeking trial, these were aggregated data that did not contain any potential confounding variables for purposes of analysis. Indeed, a multivariate model that could control for baseline and follow-up characteristics would lead to adjusted odds ratios with 95% confidence intervals and more precise and accurate inferences. Those analyses would have been performed and reported if confounders and characteristics were present in the data. However, the FDA issued the redacted version of the adjudication database, making it impossible to dig further. Finally, it might be noted that pharmacogenetics is now a practical consideration, and treating only those who have the potential to respond is starting to become more common. Further, better prospective studies should compare hard vascular outcomes between different types of bleeding groups and a no bleeding group.

CONCLUSION

These uniformly adjudicated outcome data from the PLATO trial reveal that within 12 months of DAPT, 1 out of 5 patients experience clinically relevant bleeding event, a frequency that far exceeds usually reported rates. Bleeding events across a wide specter of severity were associated with diminished incidences of death and MI and less impact on stroke. These data may advance our understanding of how to optimize DAPT strategies in the future in patients after ACS.

ACKNOWLEDGMENTS

We have met authorship criteria according to the International Committee of Medical Journal Editors criteria. Dr Serebruany takes responsibility for the integrity of the work as a whole, and Dr. Heidel was in charge of statistical analyses. Special thanks to Drs Tom Marciniak and Stuart Spencer for their critical reviews and suggestions.

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