fortune Journals

Research Article

FORTUNE JOURNAL OF HEALTH SCIENCES

ISSN: 2644-2906

Patterns of Event Adjudication in the United States PLATO Trial Cohort

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Abstract

Objective: To compare patterns of central event adjudication in the United States (US) versus the Rest of the World (RW) within the indication-seeking *Platelet Inhibition* and *Clinical Outcomes* (PLATO) trial assessing the efficacy and safety of ticagrelor versus clopidogrel in patients with acute coronary syndrome.

Background: Adjudication in randomized, outcome-driven trials is intended to maintain integrity by applying uniform rules for the quality assessment of clinical events. However, despite the reported ticagrelor benefit in the RW the US PLATO outcomes were inverted lacking reasonable explanation.

Methods: We analyzed the FDA-issued PLATO adjudication dataset, focusing on potential treatment favoritism, the impact of disagreements, and prevailing diagnostic decisions in the US versus the RW.

Results: Among 18,624 (1,413 US) trial enrollees 10,705 (1,003 US) events occurred across 7,171 (973 US) patients. There were 938 deaths (53 US), 2,752 (242 US) MI's, 367 strokes (23 US), and 3,822 (368 US) bleedings. Matches occurred for 7,240 events (653 US), while mismatches favoring clopidogrel (n = 1,715) or ticagrelor (n = 1,708) (p = 0.195) were common across major (n = 1,789), moderate (n = 932), and minor (n = 727) disagreements. The central diagnostic decision prevailed in 2,945 cases (295 US). Significant adjudication favoring ticagrelor was observed for bleeding (HR = 1.17; CI: 1.01–1.35; p = 0.037), trends for vascular death (HR = 1.20; CI: 0.64–2.25), MI (HR = 1.31; CI: 0.96–1.78), and stroke (HR = 2.04; CI: 0.62–6.70) in the US. Adjudication disagreements for combined primary events heavily favored ticagrelor in the US compared to the RW (HR = 1.35; CI: 1.16–1.56; p = 0.03).

Conclusion: Ticagrelor favoring in the PLATO-US cohort adjudication suggests unblinding. Among all countries, the CRO - monitored PLATO-US site-reported, but not adjudicated outcomes, represent the largest and most reliable dataset of realistic verified evidence suggesting ticagrelor inferiority to clopidogrel.

Keywords: Event adjudication; United States; Clinical trial; Bleeding; Death; Myocardial infarction; Stroke.

Key Findings

1. Overall, adjudication in the PLATO-US cohort was unremarkable, with the exception of primary endpoint components, bleeding events, and the severity of disagreements, compared to the Rest of the World within the same PLATO indication-seeking trial.

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Citation: Victor Serebruany, Hector A, Cabrera-Fuentes, Wendy Ziai, Efrén Emmanuel Jarquín González, Isabella Hwang, Wiktor Kuliszkowski, Dan Hanley. Patterns of event adjudication in the United States PLATO trial cohort. Fortune Journal of Health Sciences. 8 (2025): 968-974.

Received: October 08, 2025
Accepted: October 15, 2025
Published: October 27, 2025

Serebruany V, et al., Fortune J Health Sci 2025
DOI:10.26502/fjhs.359

1. Vascular deaths, MIs, strokes, and especially bleeding were all adjudicated in favor of ticagrelor, indicative of the ICAC leadership unblinding.

1. Among all countries, the CRO-monitored PLATO-US site-reported, but not adjudicated outcomes, represent the largest and most reliable dataset of comprehensive verified evidence suggesting ticagrelor inferiority to clopidogrel for all primary endpoint components, including vascular death.

Introduction

Central event adjudication in randomized controlled megatrials is common for multicenter, international, outcome-driven studies. Delegating such a critical mission for the final assessment of the site-reported events should fix the variability of definitions, contribute to comprehending and resolving complicated clinical scenarios, and remove "noise" and potential bias from the totality of evidence [1-3]. However, whether or not the central adjudication is always justified and unbiased is still unclear. The *PLATelet Inhibition and Clinical Outcomes* (PLATO) trial enrolled 18,624 patients with unstable angina or myocardial infarction (MI) treated with coronary stenting or managed medically. The patients were randomized to receive ticagrelor 180 mg loading followed by 90 mg twice daily or clopidogrel 300-600 mg loading followed by 75 mg once daily, for up to one year [4]. The primary endpoint was defined as a combination of vascular death, including bleeding fatalities, MI, and stroke. These events occurred in 11.7% of patients from the clopidogrel arm, compared to 9.8% of ticagrelor-treated patients (HR=0.84; CI=0.77-0.92; p<0.001) (4). However, the published trial results [5,6] were challenged by the Food and Drug Administration's (FDA) Secondary Review [7] and a Review of Complete Response [8]. Further, the alleged clinical benefit of ticagrelor has also been questioned by misreported mortality timing, causes, and vanished fatalities [5,9,10], "friendly" pool of central adjudicators and International Central Adjudication Committee (ICAC) leadership [11,12], and involvement of sponsor representatives in the adjudicator selection [7,8]. Recent FDA-issued evidence suggest that central adjudication in PLATO was deliberately delayed and impacted the primary endpoint by inflating ticagrelor benefit [5,11,12] resulting in drug approval. Moreover, PLATO outcomes in the United States (US) were inverted to ticagrelor's inferiority over clopidogrel [7,8,13]. However, several critical pieces required to define the precise patterns of central adjudication in the PLATO-US cohort were still missing, since FDA clinical reviews lack site-reported US events analyses. We compared the patterns of central event adjudication in the US versus the Rest of the World (RW) in PLATO.

Methods

Data Retrieval

We filed a legal complaint in the US Federal Court (case 1:21-CV 01572 BAH), reached a Joined Status Report Order with the FDA and Department of Justice based on the Freedom of Information Act law. The FDA issued over 800 pages of evidence, and among other documents, we were provided with the entire PLATO adjudicated event listings submitted to the FDA by the ticagrelor sponsor. All events were identified by country, enrolling site, patient ID, timing, and results of adjudication, disagreements, mismatches in diagnoses, etc.

Patients

Study participants and procedures are described in detail elsewhere [4,7,8]. Patients were enrolled if they presented with recent onset (no more than 24 hours) of ACS. Among major exclusions were contraindication against clopidogrel, fibrinolytics, oral anticoagulants, the bradycardia risk, or concomitant use of a strong cytochrome P-450 3A inhibitor or inducer. Overall, 18,624 patients were enrolled, about a quarter were diabetics, over 60% underwent stent implantation, 10% underwent heart surgery, and 46% received prehospital clopidogrel. The follow-up duration was restricted to 1 year. However, 23% of participants stopped taking the study drug before the end of follow-up, most frequently due to repeated bleeding or dyspnea [7,8].

Events

Most adjudicated events, such as death, MI, stroke, and bleeding, have been defined and described in detail [4,7,8]. Briefly, each event was characterized by an adjudication code. The ICAC evaluated data of every patient designated by a local investigator as a possible event, and also all patients who underwent heart surgery during the study. The ICAC determined that some events reported by Investigators did not qualify. On occasion, the ICAC identified additional unreported events to query a site to register the event for official adjudication. If the local Investigator agreed, the event was registered and processed by the ICAC.

Adjudication Database

The FDA-issued database spreadsheet contains 10,705 events. Each event is marked by a trial unique identification number, country, enrolling site, patient age, gender, treatment assignments, discontinuations, outcome codes, precise dates, and causes of trial entry and exit. In addition, enrollment codes, event tracking numbers, and patient participation in Holter, pharmacokinetics, and pulmonary function sub-studies were also provided. Final adjudicated event results (CADJRES) were coded as 1-death; 2-myocardial infarction; 3- stroke; 4 - recurrent ischemia; 5 – severe recurrent ischemia; 6-

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fatal/life-threatening bleed; 7- major bleed; 8 – minor bleed; 9 – minimal bleed; 10 – no event; 11 – transient ischemic attack;12 – arterial thrombotic event; and 99 – withdrawal of consent. Exact classifications and subtypes of death, MI, and stroke were also provided for each entry.

Disagreements

These were identified by the mismatch between event classification from the local site and central adjudication. The FDA provided full disclosure of such mismatches, including event details from the site, final adjudication results, disagreement dates, resolution by reviewers or committee (if any), and disagreement severity (minor, moderate, or major), type, and details.

Statistics

The significant differences were defined when a two-sided alpha value was less than 0.05, uncorrected for multiple comparisons. Categorical data were assessed by frequency and percentage statistics. Unadjusted odds ratios (OR) with 95% confidence intervals (95% CI) were calculated and interpreted for all chi-square tests. Unpaired t-test with Welch's correction has been applied to establish the disagreement differences. A chi-square test was conducted to evaluate the significance of the observed shift towards ticagrelor "benefit." The null hypothesis (H_0) posits that the observed shift is due to random chance alone (sporadic), while the alternative hypothesis (H_1) suggests that the observed shift is not solely attributable to random chance (non-sporadic). All analyses were performed using SPSS Version 28 (Armonk, NY: IBM Corp.), with the exception of the forest plot, which was constructed in GraphPad Prism Version 8.0.0 (San Diego, CA: USA).

Results

Among 18,624 (1,413 US) trial enrollees 10,705 (1,003 US) events occurred across 7,171 (973 US) patients. There were 938 deaths (53 US), 2,752 (242 US) MI's, 367 strokes (23 US), and 3,822 (368 US) bleedings. The comparison of the site-reported and adjudicated events in the US versus the RW is shown in **table 1.**

Overall, the reporting patterns of the US-PLATO cohort were not remarkable with few exceptions. Almost all types of events were reported more frequently by US sites, especially obvious for bleeding, MI, and cardiac ischemic events, in contrast to fewer deaths and strokes than in the RW. The adjudication results were also slightly different. Over one hundred MIs in the US were not adjudicated and dismissed, contributing to the excessive "no event" category. The USA had more cases dismissed (21.66%) vs. RoW (16.63%), indicating stricter adjudication in the USA. We then triaged the refused events dependent on the treatment arm. These data are summarized in **table 2.** The distribution of refused unadjudicated events was unremarkable in the

Table 1: Event reporting and adjudication in the United States versus the Rest of the World in PLATO.

Event	US – Sites n (%)	US - Adjudicated n (%)	RW - Sites n (%)	RW - Adjudicated n (%)
Arterial thrombotic event	13 (0.92%)	2 (0.14%)	118 (0.69%)	58 (0.34%)
Bleeding	368 (26.04%)	352 (24.91%)	3454 (20.07%)	3318 (19.28%)
Cardiac ischemic event	304 (21.51%)	136 (9.62%)	2391 (13.89%)	1126 (6.54%)
Death	53 (3.75%)	53 (3.75%)	885 (5.04%)	885 (5.14%)
Myocardial Infarction	242 (17.13%)	134 (9.48%)	2510 (14.58%)	1166 (6.77%)
Stroke/TIA	23 (1.63%)	20 (1.42%)	344 (2.00%)	287 (1.67%)
No Event	-	306 (21.66%)	-	2862 (16.63%)
Total	1003 (100)	697 (69.5%)	9702 (100%)	6840 (71.6%)

Table 2: "No event" distribution between the US and the Rest of the World.

Site Events not Adjudicated	USA - Ticagrelor	USA - Clopidogrel	Rest of World - Ticagrelor	Rest of World - Clopidogrel
Arterial Thrombotic	5 (3.45%)	4 (2.68%)	29 (2.10%)	30 (2.05%)
Bleeding	8 (5.52%)	6 (4.03%)	74 (5.35%)	61 (4.16%)
Cardiac Ischaemic	35 (24.14%)	29 (19.46%)	158 (11.42%)	156 (10.65%)
Myocardial Infarction (MI)	96 (66.21%)	108 (72.48%)	1098 (79.39%)	1186 (80.96%)
Stroke/TIA	1 (0.69%)	2 (1.34%)	24 (1.74%)	32 (2.18%)
Grand Total	145	149	1383	1465

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US when compared with the RW dataset. Indeed, there were no treatment arm preferences in the "no event" category in PLATO. Since the ticagrelor mortality "benefit" represents the most important piece of evidence, we focused on the distribution of causes of death in countries monitored not by the ticagrelor sponsor, but by independent Clinical Research Organizations (CROs).

Data in **table 3** indicate that among independently monitored countries in Georgia, Israel, Russia, and Ukraine, the deaths classifications underwent only minor changes, even slightly favoring clopidogrel with regard to the primary outcomes count. However, for the US, the picture is different. That is especially obvious looking at the FDA-adjudication dataset column D_SCOM, indicative of whether the disagreement between the principal investigator and ICAC was solved. Overall, there are 15 inquiries (9 clopidogrel and 6 ticagrelor) to question the death category in the US. For the US, there are 4 cases (lines 894,899,901 and 917) with the "NO" agreement has been reached. All these deaths were switched to vascular and all belong to the clopidogrel arm. There are only 20 rare "NO" agreements at D_SCOM entire column total among thousands of reported events. Also, D_DAT column (date of adjudication) indicates that all the deaths were adjudicated very late in the trial. We then analyzed the PLATO-US primary endpoint composition based on site-reported versus adjudicated events (**figure 1**).

In fact, the ticagrelor inferiority in PLATO-US is more profound than considered based on the FDA-generated Kaplan-Meyer curves (A). There is an early separation of the curves and consistently worsened outcomes after ticagrelor. The patterns of PLATO-US adjudication focusing on treatment assignments are exposed in **figure 2.**

With regard to favoring, there was a consistent shift towards ticagrelor advantage for bleeding, cardiac ischemic events, vascular death, MI, and heavy adjudication disagreements. There was highly significant disagreement favoring ticagrelor (HR=2.02; CI:1.1-3.64; p=0.019) for the adjudicated combined primary endpoint events.

Table 3: Site-reported versus adjudicated deaths in the CRO-monitored countries in PLATO.

Country*	Ticagrelor V/NV/U	Clopidogrel V/NV/U	Ticagrelor V/NV/U	Clopidogrel V/NV/U	Potential Bias
Georgia	11/0/1	7/0/0	12/0/0	7/0/0	No
Israel	05-04-2000	06-05-2001	06-03-2000	07-05-2000	No
Russia	21-03-2005	18-01-2000	23-02-2004	17/0/2	No
Ukraine**	4/0/0	06-01-2000	4/0/0	06-01-2000	No
USA	19-05-2005	14-06-2004	22-04-2003	19-04-2001	Yes

*Germany excluded due to mixed CRO/sponsor site monitoring;
**Ukraine was included since CRO-monitored sites are presented separately;
V -vascular; NV - non-vascular; U – unknown.

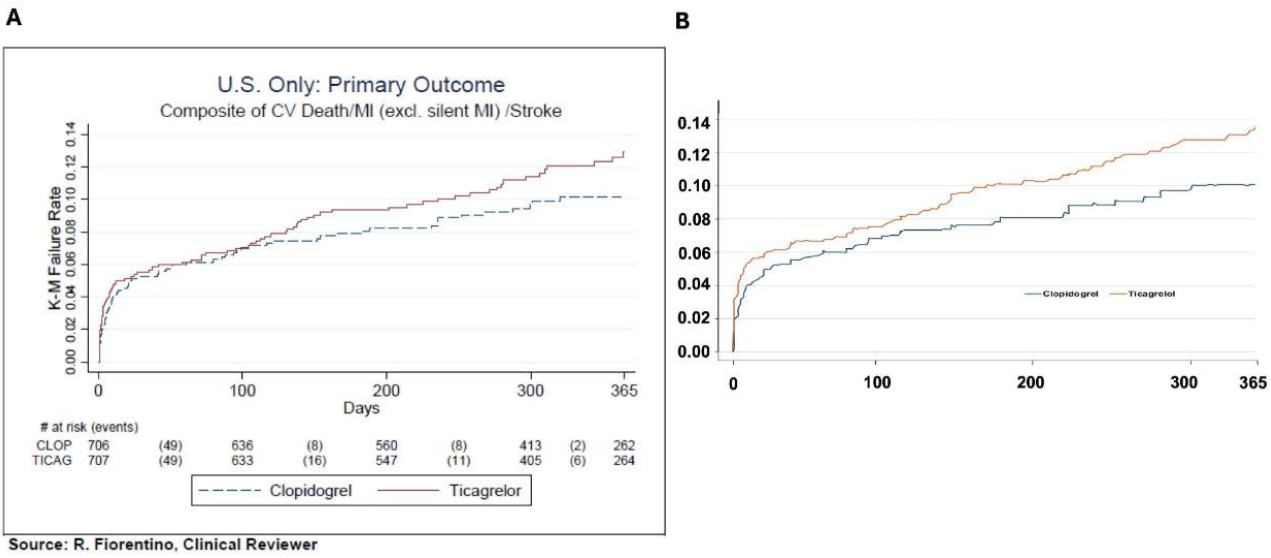

Figure 1: Adjudicated (A) versus site-reported(4) (B) primary endpoint events in PLATO-US.

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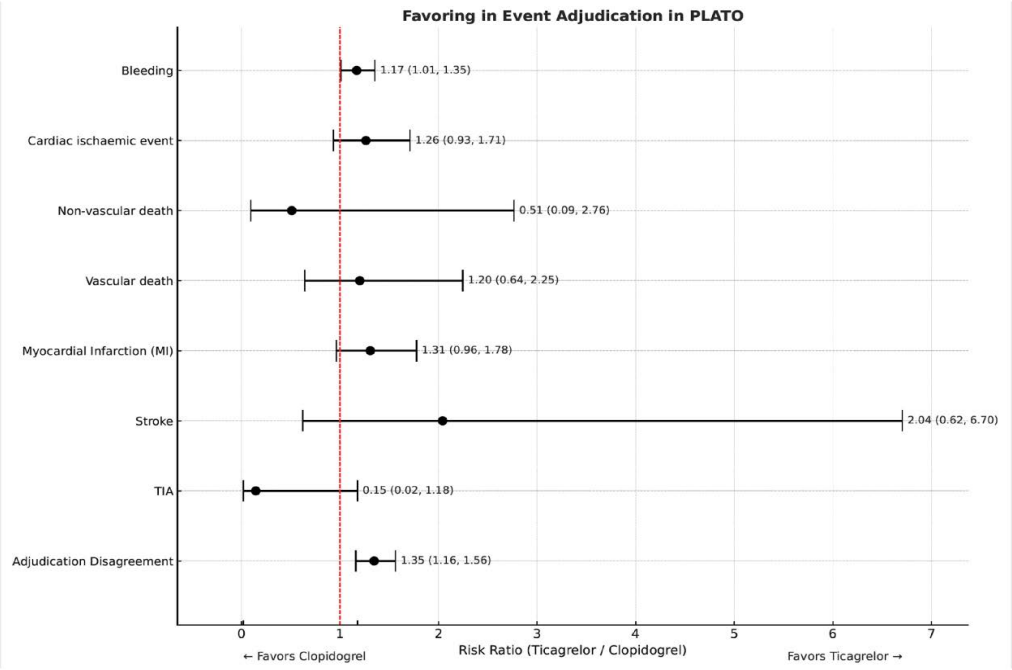

Figure 2: Treatment arm favoring of event adjudication in PLATO-US.

Discussion

The main finding of this analysis is that the PLATO-US data were of special attention, and ICAC was focused on "repair" of woeful ticagrelor outcomes, specifically in the United States. Obviously, the FDA ticagrelor approval was challenging because of devastating PLATO-US outcomes. Therefore, the critical role of central event adjudication is impossible to underestimate, and it is entirely unclear why the FDA analyzed only the adjudicated events [7,8] but not site-reported outcomes in the United States. Should such outcome comparison occur, there would be no reason for the endless and unjustified aspirin dose speculations in the desperate attempt to "explain" and neglect PLATO-US outcomes. In reality, ICAC was most likely unblinded and deliberately adjudicated events in favor of ticagrelor. The curves for the primary endpoint difference separate early and exhibit consistent clopidogrel benefit over ticagrelor for all three primary efficacy components of (vascular death, MI, and stroke). Should these data become available to the Data Safety Monitoring Board, governed by the American scientists, most likely, PLATO will be stopped early and fairly judged as a negative trial. Therefore, deliberate massive delays in event adjudication [11-13] also serve the purpose to avoid timely assessment of the outcomes and keeping the large pool of events for the desired final count at the very end of the trial and to make sure that the FDA New Drug Application submission will have merit to be considered for approval. Summarizing all available data, it seems that the site-reported United States outcomes among 1,413 patients currently represent the largest and most valuable dataset of sponsor-free pooled data, suggesting ticagrelor inferiority to clopidogrel for all PLATO primary endpoint components. Since the safety profile of ticagrelor is poor, especially considering excess bleeding and double-digit dyspnea rates, the miracle of "mortality benefit" deserves special attention. Importantly, such deaths benefits were reported exclusively in the sponsor-controlled countries [5]. In contrast, the CRO-monitored sites consistently reported more ticagrelor deaths than after clopidogrel in the US (29/24), Russia (29/19), and Georgia (12/7), but not in Ukraine (5/6), for a total of (75 vs. 56, $p<0.01$). The CRO-monitored cites revealed no ticagrelor mortality benefit for any clinical cohort dissected by 14 vascular and 9 non-vascular PLATO death codes [5].

Moreover, now the evidence is confirmed by the independent yearlong *British Medical Journal (BMJ)* investigation that some causes, precise timing and actual event occurrences [14] and key platelet studies [15,16] were inaccurately reported by the sponsors favoring ticagrelor. In short, the differences between reporting sources are striking, and indicative that declared and currently accepted ticagrelor benefits are grossly exaggerated and derived exclusively from the sponsor-controlled PLATO sites. The fact that such a wrong message was dragged into the decade-long national ACS recommendations generated by the PLATO proxies is alarming and deserves further scrutiny and comprehension. The fact that ICAC was paying special attention to the US PLATO outcomes is obvious considering the excess quantity of disagreements, including 4 direct conflicts when American

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investigators disagree with the ICAC cause of deaths decisions in all 4 clopidogrel cases (lines 894,899,901 and 917) favoring ticagrelor via switching obvious non-vascular or unknown fatalities into vascular deaths. Obviously, the ICAC was desperate to improve the ticagrelor deaths outlook considering extremely heavy challenges of death causes. Overall, there were 15 excessive inquiries (9 clopidogrel and 6 ticagrelor) to question the death category in the US.

This paradoxical evidence makes no sense, and no alternative explanation unless American cardiologists are less qualified than their colleagues in the RW. In fact, both deaths and MIs were less common in the PLATO-US cohort than in the RW, supporting higher standards of cardiology in the United States. Finally, the recent in-depth investigation by the *BMJ* team confirmed our initial allegations and made ticagrelor future really bleak. Any further allegations that we are pursuing a "personal vendetta" or acting on behalf of ticagrelor completion are now meritless since the evidence underwent scrutiny by journalists, editors, statisticians, fact-checkers, and lawyers. Moreover, the *BMJ* discovered extra cases of deaths misreported in PLATO [14], and questionable changes in the primary endpoint definitions and gross misconduct in the ticagrelor FDA-submitted platelet studies [15]. Our opponents repeatedly tried to explain these woeful findings by statistical pitfalls, data heterogeneity, and random, not deliberate, misreporting mistakes. However, the more we know about PLATO, the less science can be applied. It seems the trial results were well preplanned before the trial started, including ticagrelor "mortality benefit", less bleeding warranted overall to substitute clopidogrel just after anticipated patent expiration. This goal was partly achieved with the heavy support of multiple proxies, including FDA leadership and key opinion leaders (especially in Europe), despite resistance from the FDA reviewers and our efforts.

Strengths and Limitations

Here are a few advantages of such analysis worth mentioning: we gained access to the governmental database that entailed mandatory event reporting. Independent specialists with expertise in outcome data mining and statistics were used to avoid any potential bias backed up by the *BMJ* investigation. The sample size for all events represents one of the largest single-trial uniform datasets containing 10,705 site-reported entries, including 1,003 in the US, allowing us to make reasonable assessments in comparing central adjudication patterns. In fact, we analyzed here a real "*terra incognita*" of clinical trials, historically keeping adjudications and especially disagreements away from the public. There are also several limitations to this study. As with any mega-indication-seeking trial, the evidence did not contain any potential individual confounding variables, making it impossible to analyze further. Applying a multivariable model that could control for baseline and follow-up variables would result in more precise and accurate inferences impacting how each individual event was adjudicated. Such analyses would have been conducted and reported if confounders and characteristics were available in the PLATO dataset. However, the FDA redacted the adjudication database, making it impossible to explore further. We also did not have any access to the ICAC communications or most local hospital records. Finally, we have no definite proof that ICAC leadership was unblinded. It is highly unlikely that such favoritism is a play of chance and deserves further investigation. Also, the ICAC was provided with biased mortality data [5,11], and it is entirely unclear why all the deaths were not inspected and all the wrong counts were later adjudicated. We conclude that the shift favoring ticagrelor in the PLATO-US cohort adjudication suggests unblinding. In reality, the ticagrelor US site reported outcomes were worse than those submitted to the FDA, representing the largest unbiased piece of evidence. Should the US events be counted properly, the ticagrelor approval chances will vanish despite FDA leadership favoritism. We fully support the latest *BMJ* leadership call for legal action [17] to protect health and serve justice.

Author contributions: VLS, DH - conception and design; WZ, IH, HACF, WK analysis and interpretation of the data; VLS, DH drafting of the paper, and revising it critically for intellectual content. All authors approved the final version to be published, and all authors agree to be accountable for all aspects of the work.

Disclosures

VLS is listed as an inventor and received compensation for the U.S. Patent Application P-17232 "Method for treating vascular diseases with prasugrel" assigned to Lilly; and "Treating Cardiac Arrhythmias, heart failure, peripheral artery disease and stroke with CYCLOPENTYL-TRIAZOLO-PYRIMIDINE or derivative thereof" (USN 61/253,829) assigned to HeartDrug™ Research. He received funding for research studies with prasugrel and clopidogrel, and consultant fees from the clopidogrel and ticagrelor manufacturers, and patent fees from Lilly and Boehringer-Ingelheim. WZ receives funds from the NIH and serves as an Associate Editor of *"Neurocritical Care",* outside the submitted work. The other authors (IH, HACF, WK, DH) have no conflicts of interest.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript. HeartDrug ™ Research LLC (Wilmington, DE, USA) paid the legal fees for the data retrieval from the FDA based on the Freedom of Information Act.

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Acknowledgements

Our true appreciation to clinical and statistical FDA reviewers on the ticagrelor New Drug Application 22-433 for their integrity and courage with the "no approval" recommendation. HACF is member of the Comité Científico de Salud de los Servicios de Salud de Oaxaca (SSO), México.

Ethical statement: The original PLATO adjudication dataset was provided by the FDA based on the Federal Court Order and Joined Status Report with the Department of Justice (Washington, D.C., USA). CONSORT checklist is not applicable since we do not report here the results of the clinical trial but rather analyze a redacted government dataset.

Data transparency: Available upon request.

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